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Targeting MYC and CDK2 in Cancer - Impacts on Senescence, Apoptosis and Immune modulation

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Front cover illustration: Co-immunofluorescent staining of T -cells (red) and Macrophages (yellow) infiltrating lung tumor mass (blue).

Targeting MYC and CDK2 in Cancer - Impacts on Senescence, Apoptosis and Immune modulation
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To My Beloved Family and Friends,

Abstract

Cancer is a disease in which cells acquire the ability to divide uncontrollably and invade other tissues. An important component of this process is the activation of oncogenes and inactivation of tumor suppressor genes. The *MYC* family of oncogenes, consisting of *MYC*, *MYCN* and *MYCL*, is frequently deregulated in human cancer, and is often associated with aggressive disease, resistance to treatment and poor outcome. *MYC* encodes a transcription factor that controls many essential cellular processes of relevance for tumor development. In this thesis, two such MYC-regulated processes have been in focus: cellular senescence and immune modulation. Previous work has shown that MYC suppresses cellular senescence, which together with apoptosis is an important barrier against tumor development. Recent studies have also shown an important role for MYC in escape from immune surveillance. Due to the central role of MYC in cancer there is an increasing interest in targeting MYC, which for a long time have been considered "undruggable". However, to function as a transcription factor, MYC needs to interact with several partner proteins. Two such proteins in the focus of this thesis are MAX and cyclin-dependent kinase 2 (CDK2). Targeting these interactions or the activities of partner proteins are plausible ways of inhibiting MYC function. This thesis centres around evaluating these two different strategies to inhibit MYC functions and develop new treatments for cancer therapy. We reported previously that suppression of senescence by MYC requires CDK2-mediated phosphorylation of MYC at serine 62, and that ablation of CDK2 activity results in senescence induction *in vitro*. In the first part of this thesis, encompassing paper I and II, we evaluated the role of CDK2 for MYC-mediated suppression of senescence and for MYC-driven tumor development *in vivo* using depletion and pharmacological inhibition of CDK2 in two MYC-driven mouse tumor models representing acute myeloblastic leukemia (AML) and lung tumors.

In paper I, we utilised a mouse AML model driven by MYC and the anti-apoptotic factor BCL-XL, Hematopoietic stem cells (HSC) purified from bone marrow cells of mice were transduced with lentiviral vectors containing MYC and BCL-XL and then transplanted into lethally irradiated mice. Untreated mice developed massive AML-like leukemia after 2-3 weeks of transplantation. The mice were treated with the CDK2 inhibitor CVT2584 or vehicle upon disease onset, either by daily intraperitoneal injections or through continuous delivery via mini-pumps. Analysis of isolated bone marrow, liver and spleen cells of mice by flow cytometry revealed a significant decrease of the leukemic AML cell population in the treated mice. CDK2 targeting reduced phosphorylation of MYC at Ser 62 in leukemic cells, significantly delayed onset of disease and improved mice survival. This was associated with induction of senescence, as measured by the decrease in proliferation, increase in senescence associated β-gal activity, $H3K9me^3$ heterochromatin foci, $p19^{ARF}$ and $p21^{CIP1}$, and activation of pRb.

In paper II, we utilized a conditional immunocompetent mouse lung tumor model induced by CRE-mediated recombination of mutant $BRAF^{V600E}$ and the MycER fusion protein through inhalation of Ad-CRE virus. In addition, MYC activity in this system is regulated by tamoxifen. These mice were cross-bred with conditional CDK2 knockout mice, to create a model where CDK2 is deleted by Ad-CRE simultaneously with activation of the two other loci. Depletion of CDK2 resulted in delayed/inhibited tumor development and significant enhancement of overall survival. This was associated with induction of senescence in tumors lacking CDK2, evidenced by reduced tumor cell proliferation and pRB phosphorylation, and induction of $p21^{CIP1}$ and H3K9me3. Similar results were obtained by pharmacological inhibition of CDK2. RNA-Seq analysis of whole lung tissue revealed that CDK2 loss counteracted MYC activity and induced the expression of genes representing the senescence-associated secretory phenotype (SASP) and genes involved in immune cell recruitment and

activation. Supporting this notion, immunofluorescence staining demonstrated an increase infiltration of T-, and B-cells and macrophages in the lungs of CDK2-deficient mice irrespective of MycER status. Further, FACS analysis of immune cell populations in the lung revealed a significant increase in CD8+ T cells, macrophages and activated NK cells, and a reduction in CD4+ T cells, in response to CDK2 depletion. Finally, examination of the effect of MYC deactivation in CDK2-depleted tumors showed a massive reduction in tumor burden. Collectively, our results demonstrate that inhibition/depletion of CDK2 inhibited AML and lung tumor development linked to induction of cellular senescence. Additionally, we uncover a promising potential role for CDK2 in modulating immune surveillance.

MAX is a dimerization partner that is essential for MYC's function as a transcription factor, and this interaction is therefore a promising target to abrogate MYC activity in cancer cells. In the second part of the thesis, covering paper III and IV, we identified and characterized small molecules inhibiting MYC:MAX interaction. Using a cell-based MYC:MAX interaction inhibitor screen employing bimolecular fluorescence complementation (BiFC) assay, we identified six compounds, named MYC:MAX inhibitors (MYCMIs), specifically reducing the BiFC signal. The effect of the compounds on MYC:MAX interaction was further validated in cells utilizing split Gaussia luciferase (GLuc), *in situ* proximity ligation assay (isPLA), co-immunoprecipitation as well as functional studies using chromatin immunoprecipitation and analysis of MYC target gene expression. This showed that MYCMI-6 and MYCMI-7 were the most potent and selective MYC:MAX inhibitors with IC50s in the single digit micromolar range. Next, we examined direct binding of MYCMI-6 and MYCMI-7 to recombinant bHLHZip domains of MYC and MAX *in vitro*, using microscale thermophoresis (MST) and surface plasmon resonance (SPR) assays. The results showed that MYCMI-6 and MYCMI-7 both bound directly and selectively to MYC with a K_D of 1.6 and 4.3 μM, respectively, but did not bind MAX to any greater extent. Analysis of MYC expression showed that MYCMI-7 reduced MYC protein levels while MYCMI-6 did not. Evaluation of the inhibitory effects of MYCMI-6 and MYCMI-7 on MYC-dependent cell growth showed that MYC-expressing transformed cells were highly sensitive, while MYC-null cells were largely unaffected. Further, MYCMI-6 and MYCMI-7 strongly reduced growth/viability of different MYC-driven cancer cell lines, including MYCN-amplified neuroblastoma and Burkitt's lymphoma cells at single digit μM concentrations, and significant correlation between MYC mRNA/protein levels and the sensitivity to treatment was observed in the NCI-60 human tumor cell line panel. Importantly, both compounds caused growth arrest but did not have cytotoxic effects on normal cells. Finally, treatment with MYCMI-6 and MYCMI-7 *in vivo* using an MYCN-amplified neuroblastoma xenograft mouse model resulted in reduced MYCN activity/expression, reduced tumor burden and massive apoptosis and necrosis in the tumor tissue, without causing severe side effects. Further experiments using MYCMI-7 treatment showed similar effects in mouse tumor models of AML and breast cancer, resulting in increased survival in the neuroblastoma and breast cancer models. The results obtained from MYCMI-6 and MYCMI-7 are encouraging and warrant further investigation with respect to their mechanism of action and the improvement of their efficacy and bioactivity for further pre-clinical/clinical development.

In conclusion, the two approaches to interfere with MYC function presented in this thesis - inhibition of CDK2 and of MYC:MAX interaction - showed promising results and can potentially pave the way for new advancements in anti-MYC cancer therapy as well as new immunotherapies.

LIST OF SCIENTIFIC PAPERS

I. **Wesam Bazzar*,** Matteo Bocci*, Eduar Hejll*, Vedrana Högqvist Tabor, Per Hydbring, Alf Grandien, Mohammad Alzrigat, Lars-Gunnar Larsson.
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Pharmacological inactivation of CDK2 inhibits MYC/BCL-XL-driven leukemia in vivo through induction of cellular senescence.
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Loss of CDK2 inhibits $BRAF^{V600E}$/MYC-induced mouse lung tumor development correlating with induction of senescence and immune response.
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*=shared first authorship
A selective high affinity MYC-binding compound inhibits MYC:MAX interaction and MYC-dependent tumor cell proliferation.
Scientific Reports, 8, 10064-10081, 2018.

IV. Alina Castell*, Qinzi Yan*, Karin Fawkner*, **Wesam Bazzar****, Fan Zhang**, Malin Wickström, Mohammad Alzrigat, Donald Cameron, Marcela Franco, Cecilia Krona, Cecilia Dyberg, Thale Kristin Olsen, Vasiliki Verschut, Ying Ting Sheryl Lim, Linnéa Schmidt, Suman Vodnala, Mårten Fryknäs, Per Hydbring, Sören Lehmann, Sven Nelander, Laura Baranello, John Inge Johnsen and Lars-Gunnar Larsson.
*=shared first authorship **shared second authorship
MYCMI-7 - a small MYC-binding compound that inhibits MYC:MAX interaction and tumor cell growth in culture and in vivo in a MYC-dependent manner.
Manuscript, 2021

CONTENTS

LIST OF ABBREVIATIONS

4EBP1	eIF4E binding protein 1
AKT	RAC-alpha serine/threonine-protein kinase
ALL	T cell acute lymphoblastic lymphoma
AML	Acute myeloid leukemia
AMPK	AMP-activated protein kinase
APCs	Antigen-presenting cells
ATM	Ataxia-telangiectasia-mutated
AURKA	Aurora kinase A
AUF1	AU-rich element RNA-binding protein 1
BAD	Bcl-2 associated death promoter protein
BAK	Bcl-2 homologous antagonist killer
BAX	Bcl-2 associated X protein
BCL-2	B cell lymphoma 2
BCL-XL	B cell lymphoma extra large
BET	Bromodomain and Extra-Terminal motif
BHLHZip	Basic helix-loop-helix/leucine zipper
BID	H3 interacting-domain death agonist
BiFC	Bimolecular fluorescence complementation
BIM	Bcl-2-like protein 11
BrdU	5-bromo-2'-deoxyuridine
C/EBPβ	CCAAT/enhancer binding protein-β
CAFs	Cancer-associated fibroblasts
CAK	CDK-activating kinase
Caspases	Cysteine-aspartic proteases
CCL	C-C motif chemokine ligand 2
CD	Cluster of differentiation
CDC6	Cell division control protein 6 homolog
CDC25	M-phase inducer phosphatase
CDK	Cyclin-dependent Kinase

CIP2A	Cancerous inhibitor of PP2A
ChIP	Chromatin immunoprecipitation
CHK2	Checkpoint kinase 2
CML	Chronic myeloid leukemia
CSF	Colony stimulating factor
CTD	C-terminal domain
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
Cul1	Cullin1
CXCL	Chemokine (C-X-C) motif ligand
CXCR	CXC chemokine receptor
DCs	Dendritic cells
DDR	DNA damage response
DISC	Death-inducing signalling complex
DNMT3a	DNA methyl transferase 3a
dNTP	Deoxyribonucleoside triphosphate
EdU	5-ethynyl-2'-deoxyuridine
EGF	Epidermal growth factor
eIF4	Eukaryotic initiation factor-4
EMT	Epithelial–mesenchymal transition
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase-1
ER	Estrogen receptor
ERK	Extracellular signal-regulated mitogen-activated protein kinase
EZH2	Enhancer of zeste 2
FADD	FAS-associated protein with death domain
FBXW7	F-box/WD repeat-containing protein 7
FGF	Fibroblast growth factor
FOXO	Forkhead box protein O
GAP	GTPase activating proteins
Grb2	Growth factor receptor-bound protein 2
GPCR	G-protein coupled receptors
GSK3-β	Glycogen synthase kinase 3 beta

H3K9me3	Histone H3 lysine 9 trimethylation
HATs	Histone acetyltransferases
HDACs	Histone deacetylases
HLA	Human leukocyte antigens
ICAM-1	Intercellular adhesion molecules-1
IFN	Interferon
IL-	Interleukin
IL-1RA	IL-1a receptor antagonist
IL-*R	Interleukin * receptor
IKK	Phosphorylating IκB kinase-α
isPLA	in situ proximity ligation assay
JAK/STAT	Janus kinase/signal transducers and activators of transcription
LAG-3	Lymphocyte activation gene-3
MAGE	Melanoma antigen-encoding
MAPK	Mitogen activated protein kinase
MAX	MYC associated factor X
MCM	Minichromosome maintenance
MDM2	Mouse double minute 2 homolog
MDSCs	Myeloid-derived suppressor cells
MEFs	Mouse embryonic fibroblasts
MHC	Major histocompatibility complex
MICA	MHC class I chain-related protein A
MIZ-1	MYC-interacting Zn finger protein-1
MMP	Matrix metalloprotease
MNT	Max's next tango
MST	Microscale thermophoresis
mTOR	Mammalian target of rapamycin
NF1	Neurofibromin 1
NF-κB	Nuclear factor-κB
NHEJ	Non-homologous end joining
NK	Natural killer

NLS	Nuclear localization signal
NSCLC	Non-small cell lung cancer
NuRD	Nucleosome remodeling deacetylase
OHT	4-hydroxytamoxifen
OIS	Oncogene-induced senescence
P53	Tumor protein P53
P-TEFb	Positive transcriptional elongation factor b
PAK	p21-activated protein kinase
PCA	Protein-fragment complementation assay
PDAC	Pancreatic ductal adenocarcinoma
PDGFR	Platelet-derived growth factor receptor
PDK1	Pyruvate dehydrogenase kinase 1
PD-L1	Programmed death-ligand 1
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol-4, 5-bisphosphate
PIP3	Phosphatidylinositol-3, 4, 5-triphosphate
PKM2	Pyruvate kinase M2
PP2A	Protein phosphatase 2A
pRB	Retinoblastoma protein
PRPS2	Phosphoribosyl pyrophosphate synthetase 2
PTEN	Phosphatase and tensin homologue
RAF	Rapidly accelerated fibrosarcoma kinase
REFs	Rat embryonic fibroblasts
RNAP II	RNA Polymerase II
ROS	Reactive oxygen species
MEK	Mitogen-activated protein kinase kinase
RPS14	Ribosomal protein S14
RTK	Tyrosine kinase receptors
rtTA	Reverse tetracycline-controlled transactivator
SAHF	Senescence-associated heterochromatin foci
SASP	Senescence-associated secretory phenotype

SA β-GAL	Senescence-associated β- galactosidase
SCLC	Small cell lung carcinomas
SET	Inhibitor-2 of protein phosphatase-2A
SHH	Sonic hedgehog
SIRTs	Sirtuins
SKP2	S-phase kinase associated protein 2
SOS	Son of sevenless
SPP1	Secreted phosphoprotein 1
SPR	Surface plasmon resonance
STAT	Signal transducer and activator of transcription proteins
TAM	Tumor -associated macrophages
TFIIH	Transcription factor IIH
TGF-β	Transforming growth factor beta
TILs	Tumor infiltrating lymphocytes
TIS	Therapy-induced senescence
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRADD	TNF receptor-associated death domain
TRE	Tet response element
Treg cells	Regulatory T cells
tRNA	Transfer RNA
TSS	Transcription start site
TSG	Tumor suppressor gene
ULBP	UL binding protein
VEGF	Vascular endothelial growth factor
VHL	Von Hippel–Lindau
WNT	Wingless/Integrated
WRN	Werner syndrome ATP dependent helicase
XCL1	Chemokine (C motif) ligand 1
XIAP	X-linked inhibitor of apoptosis protein
YFP	Yellow fluorescent protein

1 Introduction

1.1 Cancer Biology

Cancer, which is another term used to describe malignant tumors, is one of the leading causes of death around the world, with over than 1.8 million new cases and over 600,000 deaths in the USA alone during 2019 (Siegel, Miller, & Jemal, 2020). It's a disease which arises when cells gain uncontrollable capacity to divide and eventually invade other organs within the body, resulting in organ failure and ultimately leading to death. Cancer is a result of genetic mutations and epigenetic changes which occur due to errors in DNA replication and/or DNA damage by environmental factors during our lifetime. These factors include exposure to radiation, such as UV-radiation, and chemical compounds that can cause genetic mutations, termed carcinogens, found in tobacco smoke, for example (Borek, 1993)(World Health Organization, 2018). Other environmental factors include among others, physical agents, such as cobalt or other heavy metals, dietary factors, like aflatoxin B1 and biological agents, for instance, human papilloma virus and Kaposi sarcoma virus (Bast, 2000; Ljubojevic & Skerlev, 2014; Park, Bae, Nam, & Yoo, 2008; Weiss & Boshoff, 2000). Mutations accumulated due to exposure to these agents over a life span may lead to cancer development. A subset of cancers, 5-10%, arise from genetic mutation in the germline that are inherited, thus called hereditary cancers (National Cancer Institute, 2015). Individuals with these germline mutations are predisposed to cancer development, which often manifest early on in life. During both the hereditary and non-hereditary cancer development process, the genetic mutations acquired by the cancer cells render them irresponsive to normal cell regulation mechanisms and allow them to gain certain capabilities that boost their growth and survivability. These include many capabilities, or hallmarks, which were originally proposed and expanded on by Robert Weinberg and Douglas Hanahan. For instance, tumor cells gain the ability to proliferate without the need for external growth signals (self-sustained proliferative signalling) and acquire resistance to external antigrowth signals (irresponsiveness to antigrowth signals). They also have the ability to divide indefinitely (immortality), cell death escape, stimulate the growth of new blood vessels (angiogenesis), evade recognition and destruction by the immune system and can invade distant tissues (metastasis) (Hanahan & Weinberg, 2011).

Over the last 50 years or so, different types of therapies to combat cancer have been developed, some of which have been quite successful, but most advanced, metastatic cancers are still incurable. Traditional cancer therapies primarily consist of chemotherapy, radiotherapy and surgical removal. In chemotherapy, the patients are given one or several chemotherapeutic agents that kill dividing cells. These agents are not specific and also affect normal cells, which results in many side effects. Additionally, resistance to these chemotherapeutic agents is often observed in cancer cells, giving rise to more aggressive tumors (Fernando & Jones, 2015). The other line of cancer treatment consists of the use directed ionizing irradiation to kill cancer cells, often in combination with chemotherapy or after surgical removal of the tumor mass. Despite its localized toxic effect, due to its nature, radiotherapy can cause new mutations in normal cells and the subsequent development of new tumors (Drooger et al., 2015). Lastly, the conventional cancer

therapy approach includes surgery, in which the tumor mass is surgically removed. While less toxic than chemotherapy and radiotherapy, the size and location of the tumor, such as vicinity to vital organs, set limitations for this procedure. In addition, if metastatic spread of the tumor has occurred, surgery will not be effective. These issues highlight the need for less toxic and more effective therapies to improve the outcome for cancer patients. During the past decade, the better understanding of cancer biology led to a surge in the development of new promising cancer therapies, such as targeted therapy and immunotherapy, opening the way to achieve better and more robust cancer therapies. Following this brief introduction on cancer, I will proceed to go more in details on different aspects in cancer and tumor biology, as well as a potential new therapy, that are the focus of this thesis.

1.1.1 Cell signal transduction

To better understand some of the mechanisms involved in the process of carcinogenesis that I will discuss later in this introduction, it is vital to understand the process of cellular signal transduction. Signal transduction is the mechanism in which cells respond to external stimuli from surrounding environment and transmit the signal into the cell interior through a cascade of events and convert it into functional cellular activities. It is through this mechanism that cells initiate cellular processes such as proliferation, growth and cell migration. This process is dependent on small molecules that cells produce called ligands, which for instance can be growth factors, hormones or cytokines. These ligands, once secreted outside of the cell, can recognize and bind specifically to cell surface proteins known as receptors. Once a ligand binds its receptor, it will activate an internal signalling cascade and trigger different processes within the cell. There are many different receptors expressed on the surface of different cells, such as receptor tyrosine kinases (RTK), Frizzled family receptors, NOTCH receptors, nuclear receptors etc., all of which regulate cellular pathways and processes that are deregulated in cancer cells.

One of the most important cells signalling pathways that are commonly involved in different cancers, as well as of relevance to this thesis work, is the RAS pathway. The RAS protein belongs to the small GTPase involved in mitogen-activated signalling transduction in mammalian cells. This pathway is activated in response to many mitogenic signalling molecules such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF) through cell membrane receptors such as receptor tyrosine kinases; in these cases, the EGF receptor (EGFR), PDGF receptor (PDGFR) and IGF receptor (IGFR), respectively. RAS is activated following its binding of GTP, facilitated by guanine nucleotide exchange factors (GEFs). RAS has an intrinsic GTPase activity, which hydrolyse the bound GTP and convert it to GDP, resulting in RAS inactivation. The RAS GTPase activity is stabilized and enhanced by the GTPase-activating proteins (GAPs) for efficient deactivation (Vetter et. Al, 2001). Following its activation, RAS recruits, binds and activates several downstream effector proteins involved in different cellular mechanisms. One example of these effector proteins is RAF, found in 3 different homologous forms (BRAF, c-RAF-1 and ARAF). Once bound by RAS, the activated RAF triggers the Mitogen-Activated Protein Kinase (MAPK)/ERK pathway. Activated RAF starts a phosphorylation and activation cascade in which it interacts with and phosphorylate mitogen-activated protein kinases (MEKs) 1

and 2, resulting in their activation. MEK1/2 in turn phosphorylates and activates extracellular signal-regulated kinases (ERKs) 1 and 2. In turn, ERK1/2 proceeds to phosphorylate and activate a variety of cellular proteins, including transcription factors. One of the ERK1/2 targets is ELK1, a transcription factor from the ETS family transcription factors, which induces the expression of another transcription factor named FOS. Additionally, ERK1/2 phosphorylates the transcription factor JUN. Together, FOS and JUN form the heterodimer AP-1, a transcription factor complex involved in expression of genes required for cell cycle progression, such as *cyclin D1 (also known as CCND1)* (Albanese et. al, 1995)(Karin et. al, 1997). Furthermore, ERK promotes tRNA and 5S rRNA synthesis by phosphorylating B-related Factor 1 (BRF1), part of the RNA polymerase (pol) III-specific transcription factor (TFIIIB) complex (Felton-Edkins et. al, 2003).

Another major pathway induced by RAS activation is the phosphatidylinositol 3-kinase (PI3K) pathway. Upon activation, RAS binds PI3K through the RAS-binding domain (RBD) on the PI3K p110 catalytic subunit and leads to PI3K activation (Rodriguez-Viciana et. al, 1994). PI3K is a kinase that can phosphorylate membrane phosphatidylinositol. The PI3K protein is found as heterodimers in cells and consists of 2 subunits: a regulatory subunit (p85) and catalytic subunits (p110 α, β, γ, and δ)(Geering B. et. al, 2007). PI3K binding to RAS activates the PI3K catalytic subunit (p110), resulting in phosphorylation of the membrane-bound phosphatidylinositol-4,5-bisphosphate (PIP2) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Zhao L. et. al, 2008). The production of PIP3 results in the recruitment of AKT (also known as Protein Kinase B (PKB)), which binds preferentially to PIP3 via its plekstrin homology (PH) domain. Upon its binding to PIP3, AKT/PKB undergoes conformational change, allowing it to bind 3'-phosphoinositide-dependent kinase-1 (PDK1) (Barry and Gibbins, 2002). Following their interaction, PDK1 phosphorylates and activates AKT/PKB (Wick et. al, 2000). AKT/PKB is involved in many cellular processes. For instance, AKT/PKB has been shown to phosphorylate and inhibit Glycogen Synthase Kinase-3β (GSK3β) (Cross et. al, 1995). GSK3β is a serine-threonine kinase that is involved in β-catenin regulation, by promoting β-catenin degradation mediated by β-TRCP and the APC- Axin E3 ligase complex (Orford et. al, 1997). GSK3β inhibition by AKT/PKB allows β-catenin to escape GSK3β-mediated degradation and translocate to the nucleus, where it activates the expression of genes involved in proliferation, such as *cyclin D1* (*CCND1*) and *MYC*. Furthermore, AKT/PKB phosphorylation of GSK3β prevents the phosphorylation of MYC by GSK3β, contributing to MYC protein stability and resulting in stronger overall proliferative signal. Activated AKT/PKB phosphorylates cell cycle regulators $p21^{CIP1}$ and $p27^{KIP1}$, leading to their re-localization to the cytoplasm and freeing the CDK2-Cyclin E1 complex and promoting S phase entry (Liang et. al, 2002)(Zhou et. al, 2001). Increased protein synthesis is also required for cells in order to undergo growth and proliferation. This is regulated by the mTOR serine/threonine kinase, which consists of two core subunits: mammalian target of rapamycin complex 1 and complex 2 (mTORC1 and mTORC2, respectively). the mTOR pathway is involved in the regulation of many cellular processes, including cell growth, proliferation and survival, cell motility, cell survival, protein synthesis, autophagy, and transcription (Hay & Sonenberg, 2004). AKT/PKB stimulates translation through phosphorylation of mTORC2 on the serine 473 residue (Betz et al., 2013), and also contribute to mammalian target of rapamycin complex

1 (mTORC1) activation by blocking Tuberous Sclerosis Complex 2 (TSC2), thereby promoting protein synthesis required for cell growth (Muise-Helmericks et. al, 1998)(Gao et. al, 2004). The role of the PI3K-AKT/PKB pathway extends to regulating cell survival and apoptosis, as we will see in the section below.

1.1.2 Oncogenes and Tumor Suppressor Genes

Early research in the cancer field have identified certain genes that are involved in the process of tumor development. The functions or the regulation of these genes are often altered through different mechanisms and these alterations usually provide survival and growth advantages required for cancer cells development and maintenance. These genes are divided into two main groups based on their contributions to cancer development, termed oncogenes and tumor suppressor genes.

Oncogenes are genes driving tumorigenesis. They are usually involved in cell proliferation, growth and/or survival and become deregulated as a result of oncogenic events. Under normal physiological conditions, oncogenes are tightly controlled within the cell and are referred to as proto-oncogenes. During cancer development, these genes are deregulated, by mutations for instance, thus becoming oncogenes. They usually encode proteins that drive cell proliferation, growth and survival. While the theory of oncogenes was proposed since the early 1900s, the first oncogene to be confirmed was in 1970 by G. Steven Martin, based on Francis Peyton Rous work on v-SRC from Rous sarcoma virus (RSV) in 1911(Martin, 2001; Rous, 1911). This was shortly followed by the discovery of v-SRC homolog in humans by Michael bishop and Harold Varmus, which they named c-SRC (Stehelin, Varmus, Bishop, & Vogt, 1976). Following those discoveries, numerous oncogenes such as RAS, MYC and ERBB2 were identified and characterized. Oncogenes are deregulated in different ways; they can be overexpressed through gene duplication or acquire mutations that render them constitutively active and irresponsive to inhibitory cellular signals. An example of an oncogene that is a result of genetic mutations is RAS. RAS is frequently deregulated in tumor cells through missense mutations affecting its ability to exchange GTP for GDP, resulting in constitutively active RAS signalling. Additionally, similar genetic alterations also involved in the deregulation and activation of RAS downstream effectors, such as BRAF (Bos et. al, 1989)(Pratilas & Solit, 2010). Another mechanism in which they are deregulated is through translocations. Some translocations can result in gene fusions, where the product results in an oncogenic protein. A classic example of such translocations is BCR-ABL1 fusion gene resulting from a reciprocal translocation between q34 on chromosome 9, containing the Tyrosine-protein kinase (ABL) and part of the BCR (breakpoint cluster region) gene on chromosome 22, which gives rise to different types of leukaemia (Kurzrock, Kantarjian, Druker, & Talpaz, 2003; Pakakasama et al., 2008). These alterations provide cancer cells with a continuous proliferation signal and the blockage of apoptosis by RAS downstream effectors through the PI3K pathway. Additionally, some translocations place them under highly active promoters, for instance, and drive their high expression. An example of this is MYC, a transcription factor involved in the regulation a wide variety of cellular processes, and which will be discussed in more detail further below. Taken together, deregulation of oncogenes is a key event needed for tumor development.

The other set of important genes in the process of carcinogenesis are tumor suppressor genes, such as p53, retinoblastoma gene (RB), phosphatase and tensin homolog (PTEN) and cyclin-dependent kinase inhibitor 2A (CDKN2A) (also known as $p16^{INK4a}$). These genes give rise to proteins involved in cell cycle regulation, induction of apoptosis and/or DNA repair mechanisms. They act as ¨guardians¨ to prevent cells with abnormalities from becoming cancerous cells as they block and counter the effects of oncogenes. During the process of carcinogenesis, tumor suppressor genes are either inactivated or lose their function, an integral step towards cancer transformation. This is achieved through missense point mutations that result in a loss of function, genetic deletions of the tumor suppressor gene or via epigenetic silencing by hypermethylation of tumor suppressor gene loci, which block their expression. For example, tumor suppressor protein p53 is mutated in more than 50% of human cancers (Surget, Khoury, & Bourdon, 2013). This transcription factor plays an important role in regulating many cellular processes crucial for cell survival and tumorigenesis, in which it acts to protect cells from oncogenic transformation. p53 is involved in the activation of programmed-cell death (also known as apoptosis) and permanent growth arrest (also known as senescence), two important barriers against tumorigenesis, in response to oncogenic signals and DNA damage, which I will discuss later in this introduction. Its role in blocking tumor transformation is widely demonstrated in numerous cancer studies. For instance, it has been shown to inhibit MYC and RAS (Buganim et al., 2010; Ho, Ma, Mao, & Benchimol, 2005). Other processes inhibited by p53 is angiogenesis. Angiogenesis is controlled by the transcription factor hypoxia-inducible factor 1-alpha (HIF-1α, which regulates many genes involved in this process, including vascular endothelial growth factor-A (VEGF-A). It has been reported that p53 induces HIF-1α degradation, leading to the reduced release of VEGF-A) (Sermeus & Michiels, 2011). p53 often undergoes loss of function in cancer cells due to missense mutations in the DNA-binding domain, crippling its ability to activate genes (Levine & Lane, 2010). In addition to direct inhibition of p53 by genetic deletions and mutations, cancer cells also upregulate Mouse double minute 2 homolog (MDM2), a negative regulator that binds p53, blocks its transcriptional activity and induces p53 degradation (Fuchs, Adler, Buschmann, Wu, & Ronai, 1998; Moll & Petrenko, 2003). pRB is also found to be inactivated in many human cancers. pRB regulates the progression from G1 of the cell cycle into the S phase of the cell cycle by binding transcription factor E2F, an activator of crucial positive cell cycle regulators, preventing target gene expression. Mutated pRB loses its ability to bind E2F, resulting in S phase entry (Burkhart & Sage, 2008). Other tumor suppressor genes that are inactivated in cancer includes PTEN by genetic deletion, and CDKN2A, through hypermethylation of its promoter. PTEN is a phosphatase involved in the dephosphorylation of phosphoinositide substrates such as PIP3, thereby blocking the AKT/PKB pathway, while CDKN2A is a negative regulator of the cycle, which I will discuss in the following section (Cantley & Neel, 1999). The inactivation of oncogenes and the de-activation of tumor suppressor genes are thus crucial in the process of carcinogenesis, as such, we well explore their roles in some of these processes within the different sections of this introduction.

1.1.3 The cell cycle

During the life span if a cell, it goes through a fundamental process called the cell cycle, in which cells grow and divide. It’s a complex process that is tightly regulated and involves

many different proteins to insure a proper and viable cell division. The cell cycle can be divided into four phases: the DNA synthesis (S) phase, the mitosis and cell division (M) phase, and two growth phases in between called gap1 (G1) and gap 2 (G2). The cell cycle starts with the G1 phase, where the cell accumulates mRNA and proteins needed for the S phase. Once in the S phase, the cell duplicates its DNA content. In the next phase, G2, cells continue to synthesize cellular proteins and ensuring successful DNA replication. Following G2, the cell enters the mitotic phase. Mitosis is the process in which the replicated chromosomes and contents of the cytoplasm, duplicated during the previous phases of the cell cycle, separate, after which the cell divides into two identical daughter cells. It consists of several stages; prophase, prometaphase, metaphase, anaphase, telophase and culminating in cytokinesis to produce two daughter cells. Once completed, the cell either re-enter into G1 or go into a quiescent state called G0, in which cells stop dividing either temporarily or permanently.

As mentioned above, this process involves interplay between a variety of cellular proteins through the different phases. The main group of proteins driving the cell cycle progression are called cyclins and cyclin-dependent kinases (CDKs). Cyclins belong to a family of proteins consisting of cyclin D, E, A and B, that exhibit a varying expression pattern through the cell cycle (see below). They form complexes with CDKs during different stages in the cell cycle, a step required for the activation of CDKs and their binding to the substrates. Unlike cyclins, CDKs expression level is mostly stable through the cell cycle. While cyclins lack enzymatic activity, CDKs are a group of serine/threonine protein kinases that, once activated, act on different substrates required for cell cycle progression (Morgan, 2006). This group of proteins consist of many members, with CDK1, 2, 4 and 6 being the most crucial for cell cycle progression. Once the cell receives growth signal via its ligand-activated growth receptors, such as EGF, the consequent signal transduction results in the activation of cyclin D expression (Albanese et al., 1995). Cyclin D forms a complex with CDK4 or CDK6, which is detected by CDK-activating kinase (CAK) that phosphorylates and activates the cyclin D-CDK4/6 complex (Morgan, 2006). Once activated, cyclin D-CDK4/6 drive the cell through a mandatory check point in G1 phase, known as the R point, by phosphorylating E2F-bound pRB. The phosphorylation of pRB by cyclin D-CDK4/6 is followed by the hyperphosphorylation of pRB by the cyclin E-CDK2 complex. In its hyperphosphorylated form, pRB is inactivated and dissociates from E2F, allowing E2F to induce the expression of genes required for S phase entry (Giacinti & Giordano, 2006). During early S phase, cyclin E is replaced by cyclin A, an E2F target gene, as CDK2 partner and promote DNA synthesis initiation. Towards the end of the S phase, cyclin A-CDK2 complexs are degraded and replaced by cyclin A-CDK1 compleses that facilitates entry to the G2 phase of the cell cycle (Weinberg, 2007). During the G2 phase, when the chromosomes exit in a duplicated form, the DNA repair machinery can utilize homologous recombination to repair persisting DNA damage occurring in S phase as well as the continuation of protein synthesis in preparation for the mitosis phase. At the late G2 phase, the cell passes through the G2/M checkpoint to ensure that the DNA is repaired and ready for mitosis (Burgoyne, Mahadevaiah, & Turner, 2007). Shortly following M phase entry, cyclin A is replaced by cyclin B to form cyclin B-CDK1 complexs, which are activated by CDC25 phosphatase to guide the cell through mitosis. At the final stage of mitosis, cyclin B is degraded by Anaphase-Promoting Complex (APC) and the daughter cells exit the M phase by cytokinesis and proceed to G1 or reside in G0.

Aside from the cyclins and CDKs, another group of proteins are also actively involved in the regulation of this process. This group proteins consist of cyclin-dependent kinase inhibitors (CDKIs) belonging to two families, the INK4a family and the CIP/KIP family. The INK4a gene family includes CDKN2A (p16), CDKN2B (p15), CDKN2C (p18) and CDKN2D (p19) which mainly inhibits the cyclin D-CDK4 complex. The CIP/KIP gene family includes CDKN1A ($p21^{CIP1}$), CDKN1B ($p27^{KIP1}$) and CDKN1C (p57) and act on the CDK1 and CDK2 complexes (Weinberg, 2007). These proteins negatively regulate cell cycle progression and prevent cells from proliferating uncontrollably and are induced in response to stress signals, such as DNA damage, replication stress and aberrant oncogenic activation. For instance, oncogenic activation of RAS induces replication stress signals that activates p16 (Rayess, Wang, & Srivatsan, 2012). In turn, p16 proceeds to block cyclin D-CDK4/6 activity by binding CDK4 and preventing its association with cyclin D, blocking E2F release from pRB and halting cell cycle progression (Parry, Bates, Mann, & Peters, 1995; Serrano, Hannon, & Beach, 1993). In the case of DNA damage, DNA damage response (DDR) activates p53, which proceed to induce $p21^{CIP1}$ expression. $p21^{CIP1}$ acts by binding CDK2 and CDK1, which block their ability to form complexes with their respective

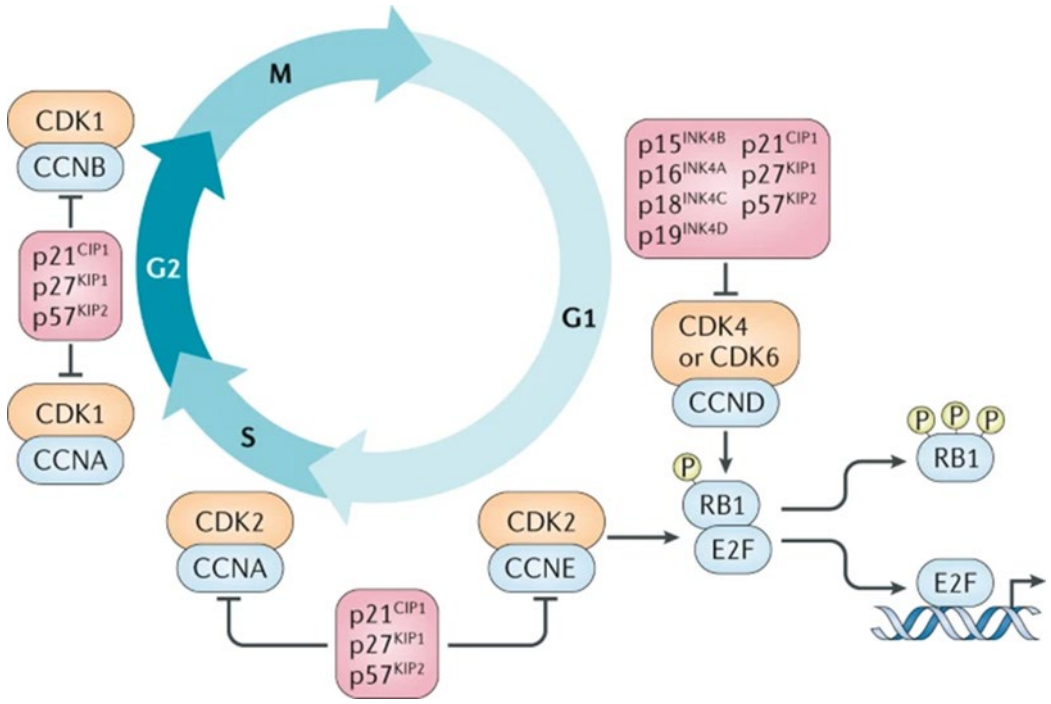

Figure 1: General schematic view of the regulation of the mammalian cell cycle. Adopted from Petroni G, Formenti SC, Chen-Kiang S, Galluzzi L.et al., Immunomodulation by anticancer cell cycle inhibitors. Nat Rev Immunol. 2020 Nov;20(11):669-679.

cyclins and advancing the cell cycle (Harper et al., 1995). In similar fashion, other CDKIs bind and block the function of different CDKs to keep malfunctioning cells from proliferating and causing diseases such as cancer. Due to their strong negative effect on cell cycle progression, CDKIs are often inactivated in cancer cells. For instance, p16 and $p21^{CIP1}$ have been shown to be inactivated in cancer cells through repressive hypermethylation marks in their promoters (Gartel et al., 2001). Additionally, positive

regulators of cell cycle progression are also deregulated in cancer. Cyclin E has been found to be deregulated and overexpressed by different mechanism in a variety of human cancers, including breast cancer and colon cancer (Donnellan & Chetty, 1999; Yasui et al., 1996). These observations highlight the importance of the cell cycle regulators and their fundamental role in cancer development.

1.1.4 Apoptosis

Over our life span, cells within different tissues get exposed to many harmful physical, chemical and biological agents. These agents cause tissue damage and can lead to dysfunctional cells capable of developing tumors. To prevent this, cells have acquired different fail-safe mechanism that are programmed to trigger cell cycle arrest or cell death in dysfunctional cells. One of these cellular mechanisms is apoptosis. Apoptosis is a process of controlled and programmed cell death, that results in clearance of malfunctioning cells, without causing trauma or damage to the surrounding cells within the tissue. This mechanism is triggered in response to stress signals, such DNA damage, oncogene-induced replication stress and viral infection. There are two main pathways to activate the apoptotic machinery; the intrinsic pathway and the extrinsic pathway (Koff, Ramachandiran, & Bernal-Mizrachi, 2015). Each of the pathways is driven by a group of proteolytic proteins called caspases. The caspases are divided into 2 groups, based on their function; initiator caspases, which includes caspase 2, 8, 9 and 10, and executioner caspases, which includes caspases 3, 6 and 7. As their naming suggests, initiator caspases facilitate the apoptotic cascade while the executioner caspases cleave and degrade the different cellular components during apoptosis. The activation of one, or both, of these pathways ultimately results in cell death.

The intrinsic pathway is triggered for instance in response to DNA damage that cells are unable to repair, for example due to replication stress or exposure to UV irradiation (Bernstein, Bernstein, Payne, & Garewal, 2002). Unlike the external pathway, this pathway does not require external cellular signals. Unresolved DNA damage triggers DDR response signalling that induces p53, which proceeds to activate the expression of several pro-apoptotic factors including BAX, BIM and NOXA. These proteins in turn translocate to the mitochondria, where they bind to anti-apoptotic factors bound to outer membrane, such as BCL-2 and BCL-X_L, causing cytochrome c release (Gross, Jockel, Wei, & Korsmeyer, 1998). Once released, cytochrome c binds to the Apoptotic Protease Activating Factor (APAF) and proceeds to cleave and activate caspase 9 (P. Li et al., 1997; Weng, Li, Xu, Shi, & Tang, 2005). Activated caspase 9 then form a complex with cytochrome c and APAF called the apoptosome, which cleave and activate the executioner caspases, resulting in the degradation of the different cellular components and cell death.

While the intrinsic pathway is a consequence of signals from within the cell, the extrinsic pathway is triggered by signal from the surrounding microenvironment. In this pathway, death receptors of the Tumor Necrosis Factor (TNF) superfamily, such as TNF-alpha receptor and FAS, are activated by TNF-alpha (TNF-α) or FAS ligand (FasL), secreted by immune cells for instance (Wajant, 2002). The intracellular domain of these receptors, termed TNF receptor-associated death domain (TRADD) and Fas-associated death

domain protein (FADD) respectively, bind and activate caspase 8 to form a complex called Death-Inducing Signalling Complex (DISC) (G. Chen & Goeddel, 2002). DISC then proceed to activate the executioner caspases, which results in cell death. The two apoptotic pathways are not always exclusive to these two initiation mechanisms, however. For example, when cytotoxic T cells and NK cells detect dysfunctional cells, such as infected cells or tumor cells, they release vesicles containing serine proteases such as granzyme B, and perforin (Everett & McFadden, 1999). Granzyme B passes through the cell membrane into the cytoplasm, which is facilitated by perforin. This cytolytic protein proceeds to cleave and activate caspases 3 and 8 to initiate the extrinsic apoptotic pathways and amplify the apoptotic cascade. Another mechanism in which both pathways get activated is through DIABLO/SMAC. This protein, like cytochrome c, is released from mitochondria following the activation of the intrinsic apoptotic pathway (Shi, 2001). Once released, it binds and inhibit the X-linked inhibitor of apoptosis protein (XIAP), an anti-apoptotic protein that binds to caspase 9 and blocks its activation. In this way, SMAC release from the mitochondria activates the ixtrinsic apoptotic pathway and enhance the programmed cell death response.

During the process of cancer development, overcoming apoptosis is one of the crucial steps that are required for malignant transformation. To achieve this, several proteins involved in apoptosis are deregulated. For instance, overexpression of the antiapoptotic BCL2 is seen in lymphomas and small cell lung carcinomas (Kaiser et al., 1996; Otake et al., 2007). BCL2 overexpression serve to block apoptosis induction due to oncogenic activation by oncogenes such as MYC. Other mechanisms to block apoptosis frequently observed in different types of cancer is through p53 inactivation, which also protect the cells from p53- induced cell cycle arrest. Another mechanism in which cancer cells often use to block apoptosis is through the PI3K/AKT pathway. AKT/PKB blocks programmed cells death through different routes. Pro-apoptotic factor BAD has been shown to be phosphorylated and inactivated by AKT/PKB (Datta et. al, 1997). Additionally, AKT/PKB phosphorylate MDM2, resulting in the subsequent p53 degradation and inhibition of p53-dependent apoptosis (Maya et. al, 2001)(Zhou et.al, 2001). Moreover, AKT/PKB induce nuclear factor-kappa B (NFκB) indirectly by phosphorylating IκB kinase-α (IKK) and leading to the dissociation of NF-κBfrom its inhibitory partner IκBα (Kane et. al, 1999). Once freed, NF-κB initiates the transcription of several genes including the anti-apoptotic factor BCL-XL and blocks apoptosis (Barkett et. al, 1999). Furthermore, AKT/PKB blocks p53-independent apoptosis by indirectly inhibiting the transcription of pro-apoptotic genes such as FasL and by the inhibition of the extrinsic apoptotic pathway (Brunet et. al, 1999)(Tang et. al, 1999). AKT/PKB also is reported to inhibit BIM and activate CREB, leading to BCL-2 induction (Pugazhenthi et. al, 2000).

Another mechanism that is considered to serve to shield and block tumor formation is cellular senescence. Senescence is a fundamental process that is involved in different biological processes, such as wound healing and tissue repair, in addition to its role in blocking cancer. This cellular response is triggered by the dysregulation of the cell cycle and involve several negative, as well as positive regulators of the cell cycle machinery. Due to its importance for this thesis work, I will discuss senescence in detail in the next chapter of this introduction.

1.1.5 Cancer and the immune system

The immune system is comprised of a variety of cells specialized in defending against pathogens, such as viruses and bacteria, but also plays an important role in cancer. The immune system is comprised of two arms, the innate and the adaptive immune systems. The innate immune system is our first line of defence against bacteria, viruses and foreign bodies, as well as cancer cells. It includes different cell types, namely granulocytes (basophils, eosinophils, neutrophils and mast cells), monocytes, macrophages, dendritic cells (DCs), as well as natural killer (NK) cells and innate lymphoid cells (ILCs). This arm of the immune system recognizes non-self molecule patterns called pathogen-associated molecular pattern (PAMPs) and danger-associated molecular pattern (DAMPs). These molecular patterns include lipopolysaccharides and endotoxins which are identified by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and c-type lectin receptors found on the surfaces of the innate immune cells. PRR activation also induces the production of cytokines, such as IL-1α, which recruit more innate immune cells into the site (Janeway & Medzhitov, 2002). The innate immune response engages in phagocytosis of the detected pathogens, as well as infected cells, by macrophages, DCs and neutrophils. Macrophages and DCs belong to a group of cells specialised in antigen processing and priming called antigen-presenting cells (APCs), which process the phagocytosed and lysed pathogens for antigen presentation on their MHC class II receptors, an important process for the subsequent activation of the adaptive immune response. NK cells on the on the other hand are a type of cytotoxic lymphocytes that rely on a phenomenon called ¨missing-self recognition¨ of MHC class I antigens to identify and kill target cells. They express activating receptors, such as NKG2D, DNAM1 and NKp46 and inhibitory receptors, such as killer cell Ig-like receptors (KIRs) on their surface. Upon contact with their target, NK cells bind to MHC class I complexes via their KIRs and to UL16 binding protein 1 (ULBP1) on target cells via NKG2D receptor. The presence of MHC class I and its binding to KIRs results in the inhibition of NK cell cytotoxic ability (Vivier et al., 2011). In virus-infected cells and cancer cells, MHC class I is downregulated, resulting in the activation of NK cells and the destruction of its target. Other cells of the innate immune system, such as basophils are involved in the recruitment of other immune cells and promotion of the inflammatory response.

The second arm of the immune system is the adaptive immunity. Unlike the innate immune system, adaptive immunity is specific in its response. It relies on the identification of specific antigen to recognize its target, which results in taking longer time for initiation. This arm of the immune system is comprised of T cells, including CD8 killer and CD4 helper T cells, as well as B cells, which includes effector B cells and memory B cells, that provides tailored response against their target. Adaptive immunity initiation is dependent on APCs from the innate immune system, as macrophage and DC presentation of antigen is a crucial step to trigger this part of the immune system. APCs migrate to the lymphoid organs, such as the lymph node, and present the antigens of the phagocyted pathogen/cell on their MHC class II molecules, which is recognized by CD4 helper T cells, leading to their activation. The activated CD4 helper T cells in turn interacts with B cells displaying the same antigen on their MHC class II complexes, which triggers the proliferation of the CD4 T helper cells, as well as B cell proliferation and maturation into memory B cells and effector B cells. The effector B cells are responsible

for the production and secretion of antibodies that bind the pathogen or infected cells that display the appropriate antigen on their surface. The memory B cells on the other hand provide long term adaptive response and immunity for the same antigen, in case of future reinfection. In addition, NK cells recognize the target-bound antibodies through Fc receptor CD16 present on NK cells surface and proceed to eliminate the target cell, which is known as antigen-dependant cell cytotoxicity (ADCC). This process provides an example of the collaboration between the innate and the adaptive immune cells, in addition to the role of APCs in initiating the adaptive response. Aside from B cell activation, the CD4 helper T cells also secrete cytokines and chemokines, such as IL-2 and interferon-γ (IFN-γ), that trigger CD8 killer T cell proliferation and the amplification of the immune response at the site. The CD8 killer T cells, also known as cytotoxic T lymphocytes (CTLs), bind its target cells via MHC class I complexes and proceed to induce apoptosis and eliminate their target (Paul, 2011; N. C. Smith, Rise, & Christian, 2019).

Beside its role in protecting against pathogens, the immune system can attack and eliminate tumor cells, protecting against cancer development. Albeit ongoing research is showing a complex dynamic interplay between the immune system and cancer cells. This has given rise to the hypothesis of immunoediting, which describes how cancer cells attempt to escape immunosurveillance, the process of monitoring and eliminating dysfunctional cells by the immune system, and eventually progress. This hypothesis emphasizes that the interaction between the immune system and cancer cells during tumor development consist of 3 distinctive states; elimination, equilibrium and escape (Schreiber, Old, & Smyth, 2011). Cancer cells are constantly adapting, through genetic or epigenetic mechanisms, to develop means to weaken the anti-tumor immune response and achieve immune escape. During the process, the balance between these phases determines the outcome between either tumor elimination and tumor escape and progression.

Different immune cells subtypes have different effect on cancer cells, as some behave in an anti-tumor fashion and aid in its elimination, while some subtypes act as pro-tumor entities and protect the tumor for immune cells killing. For a better understanding, I will first discuss the anti-tumor side of the immune system, followed by the pro-tumor side. In the T cell compartment of the immune system, cytotoxic CD8 T cells are known to have an anti-tumorigenic function. They are one of the killer cells in the immune system, specialized in eliminating infected cells as well as cancer cells. During the process of tumorigenesis, cancer cells express “neoantigens”, which are products of genetic mutations during oncogenic activation. Upon death of cancer cells, these neoantigens are released into the surrounding tissue, where they are picked up by APCs, such as resident mature dendritic cells (mDCs) (Sánchez-Paulete et al., 2017). These cells process the antigens and present them on MHC class II molecules, and upon interacting with a naïve CD4 or CD8 T cells, activate them to become CD4 T helper or CD8 cytotoxic T cells (Binnewies et al., 2019; Broz et al., 2014). These CTLs then proceed to kill cells expressing these antigens together with MHC class I by inducing apoptosis via granzyme B or the death receptor, as I discussed in the previous section. Another subpopulation of the T cell compartment involved in anti-cancer immunity is the CD4 T_{h1} helper cells. These cells can also interact with APCs, such as mDCs, through MHC class II molecules

and activate CD8 cytotoxic T cells (Umeshappa et al., 2009). These cells are also associated with recruitment of CD8 cytotoxic T cells via Th1 IFNγ-mediated CXCL9 and CXCL10 secretion by cancer cells (Peng et al., 2015). One other important player in the anti-tumor immunity response is Natural Killer (NK) cells. A common occurrence in cancer cells is the absentee of MHC class I molecules, a mechanism used to avoid detection by T -cells (Z. Wang et al., 2008). This allows NK cells to recognize and bind these cells, and to trigger apoptosis by releasing granzymes. Additionally, NK cells secrete chemoattractants, such as XCL1 and CCL5, which recruits DCs that stimulates CD8 cytotoxic T cells (Böttcher et al., 2018). Macrophages also play a role in anti-cancer immunity. Macrophages are monocyte-derived innate immune cells involved in clearing pathogen, cellular debris as well as cancer cells. These cells are further classified into M1-like and M2-like macrophages, based on the cellular markers displayed on the surface of these cells. The M1-like macrophages constitute the subset that is considered to aid against tumor development. These cells secret pro-inflammatory cytokines and chemokines, such as IL-12 and TNF-α, that attract other components of the immune system to the tumor tissue and enhance the anti-cancer immune response (Dorman & Holland, 2000; Olszewski, Groot, Dastych, & Knol, 2007). These cells are also capable of presenting antigens and aid in T cell activation for a robust immune response. Moreover, B-cells have been suggested to contribute to anti-tumor immunity through antibody-dependent cell-mediated cytotoxicity (ADCC) and the induction of NK and T cell response through IL-12- and IFNα/β-secretion (Guo & Cui, 2019). The myriad of anti-cancer immune cells highlights the importance of the immune system in the battle against cancer.

On the other hand, there are several immune cell subtypes that protect cancer cells and promote cancer progression. One of the most important components of the pro-cancer immune response is a subpopulation of T cells, CD4 regulatory T cells (Tregs). These cells are mainly involved in the regulation of T cell immune response and mitigate their self-reactivity caused by autoimmune diseases, for instance. During tumorigenesis, cancer cells recruit Tregs and trigger their differentiation, perhaps through the secretion of C-C motif chemokine 22 (CCL22) and transforming growth factor beta (TGFβ) (Lippitz, 2013). Tregs serve to suppress T cell antitumor response through multiple ways. They deplete IL-2, an important inducer of CD8 T cell proliferation, and inhibitory cytokines, such as TGF-β and IL-10, thereby resulting in the suppression of cytotoxic T cells (Collison et al., 2007; Setoguchi, Hori, Takahashi, & Sakaguchi, 2005; T. Takahashi et al., 1998). Tregs also express immune inhibitory receptors, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and lymphocyte activation gene-3(LAG-3), which further inhibits CTLs proliferation and their activation by APCs (Camisaschi et al., 2010; C. T. Huang et al., 2004). Additionally, Tregs contribute to CD39 and CD73 production, which are important for production of adenosine - a suppressor of Th1 helper and cytotoxic T cells (Maj et al., 2017). A subpopulation of macrophages also plays an integral role in pro-tumor immunity, demonstrating the plasticity of these cells during cancer development. Unlike M1-like macrophages, these Tumor-Associated Macrophages (TAMs), belong to the M2-like anti-inflammatory subpopulation. It has been shown that M2-like macrophages suppress cytotoxic T cells through expression of the inhibitory molecules CTLA-4 and PD-1 (Mihic-Probst et al., 2020). Furthermore, monocytes, a precursor of macrophages, are recruited and differentiated into the M2-like

anti-inflammatory macrophages via the secretion of colony stimulating factor 1 (CSF-1) and CCL2 by cancer cells, highlighting the importance of monocytes in cancer development (Lewis & Pollard, 2006). Beside promoting immune evasion, the pro-tumor role of M2-like TAMs extends to promotion of angiogenesis and metastasis, important hallmarks of cancer, by releasing VEGF-A, matrix metalloproteases and TGFβ (E. Y. Lin et al., 2006). Another entity involved in immune escape is myeloid-derived suppressor cells (MDSCs). MDSCs facilitate immune evasion by suppressing cytotoxic T cell function, tumor cell clearance by NK cells, recruitment of suppressive Tregs and promoting angiogenesis and metastasis (Ostrand-Rosenberg & Fenselau, 2018).
Other immune cells involved in supporting tumor progression also include neutrophils, with multiple studies indicating a role in metastasis (Szczerba et al., 2019; Tao et al., 2016). The increased knowledge about the contribution of these different immune cells to cancer progression instigated new interest in the molecular mechanisms of tumor immunology and inspired new promising therapies utilizing the immune system for cancer treatment.

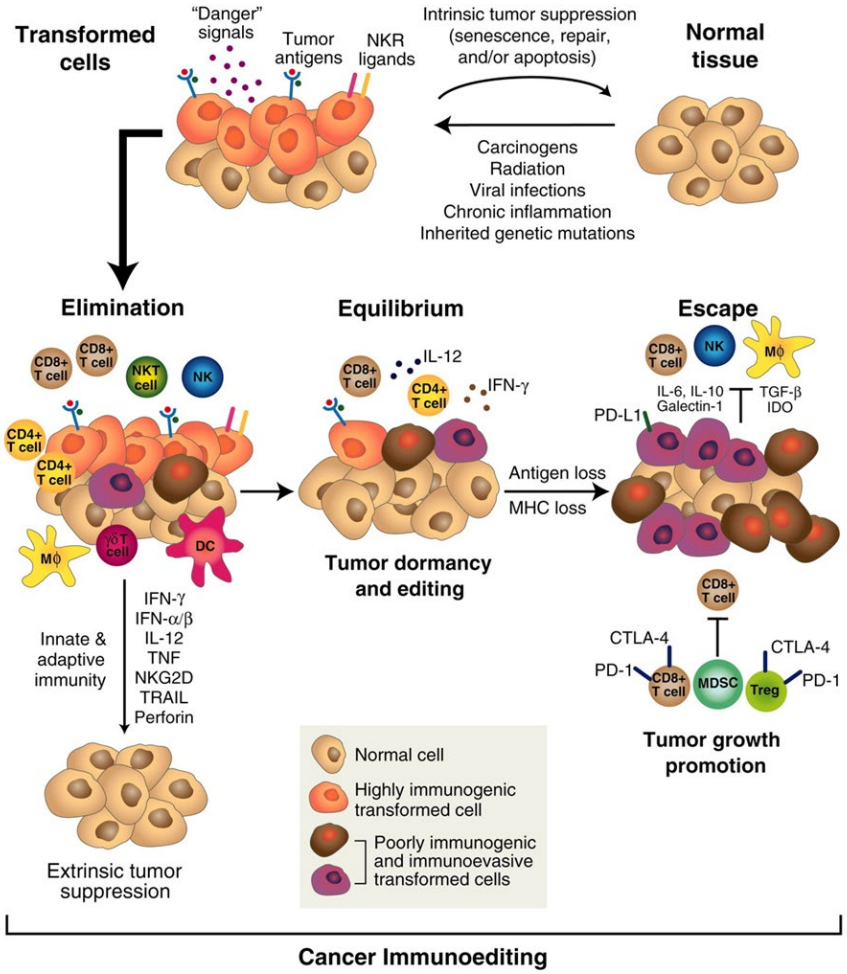

Figure 2: The concept of cancer immunoediting: elimination, equilibrium, and escape. Adopted from Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011; 25; 331:1565-1570.

During the past decade, several novel approaches for immunotherapies have been approved for treatment. For instance, the use of checkpoint inhibitors against CTLA-4 and PD-1, has been approved for treatment of malignant melanoma. These inhibitors block cytotoxic T cell inactivation via these molecules resulting in tumor elimination. Another strategy involves the use of Tumor Infiltrating Lymphocytes (TILs), that are harvested from patients. Once harvested, they are activated and propagated *in vitro* by IL-2 stimulation and reintroduced into the patient, where they actively attack and help eliminate the tumor. Moreover, the use of engineered T cells known as Chimeric Antigen Receptor-T cells (CAR-T cells) was approved in 2017 for the use in haematological malignancies. Similar to TILs, this strategy requires the purification of T cells, which are then expanded by stimulation with IL-2 and CD3. Following their expansion, the T cells are genetically modified to express chimeric antigen receptors against the patient's tumor antigens utilizing retroviral vectors and CRISPR/Cas9 technology. The cells are then administered to the patient, where they can kill cancer cells expressing these antigens. CAR-T cell treatment showed promising results in treating diffuse large B-cell lymphoma and leukemia. Despite their success in the treatment of several types of tumors, some patients did not benefit from this treatment because of weak immune response. In addition, the efficiency of CAR-T cell treatment on tumors with low immunogenicity was limited. Moreover, adoptive cell therapy, including TILs and CAR-T cells, was not as successful in treating solid tumors, mainly due to the highly immunosuppressive tumor microenvironment that negatively affected their activity and survival (M. Martinez & Moon, 2019). This suggests that these immunotherapies still suffer from limitations and challenges, requiring more knowledge and research in the field of cancer immunology.

1.1.6 Lung cancer

Due to its relevance to this thesis, I will briefly discuss lung cancer in this section. Lung cancer is the global leading cause of cancer-related deaths. According to statistics from the world health organization (WHO) approximately, a total of 2 million diagnosed cases and 1.76 million deaths were recorded in 2018 (World Health Organization, 2019). The median 5-survival of lung cancer is 10-20% and is heavily dependent on stage of diagnosis. Lung cancer is classified into two major subtypes: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC comprise most lung cancer patients and is sub-divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (Inamura, 2017), Meanwhile, SCLC account for 15 % of all lung cancer patients. NSCLC is generally less aggressive and is characterized with a lower proliferative index and metastatic rate than observed in than SCLC. The most frequent driver mutations hit KRAS (20-50%) and EGFR (10-35%), whom are usually mutually exclusive ((Herbst, Morgensztern, & Boshoff, 2018; Massó-Vallés, Beaulieu, & Soucek, 2020). In addition, other driver mutations have been identified, such as BRAF (1-5%), ERBB2/3 (10-15%), NRAS (1%), HRAS (1.6%), AKT1/2/3 (1–2%), and amplifications in MYC (33%), MET (2–4%), FGFR1 (20%), and chromosomal rearrangements in ALK (3-7%) and ROS1 (1-2%) (Q. G. Zhu, Zhang, Ding, He, & Zhang, 2017). Additionally, inactivation of p53, PTEN, ATM, CDKN2A, and RB, among others (Herbst et al., 2018; Iwakawa et al., 2011; Schaub et al., 2018). For patients with EGFR-mutated NSCLC, the treatment consists of tyrosine kinase inhibitors as the first-line treatment, with disease relapse unfortunately observed in most patients (Ricciuti et al., 2016). Targeted therapies

for KRAS are not yet available and patients undergo standard platinum-based chemotherapy as their first line treatment.

The SCLC subtype is very aggressive, with a 5-year medial survival of 1-5% and is characterized with a higher proliferation index, rapid metastatic onset and neuroendocrine phenotype (Travis, Brambilla, Burke, Marx, & Nicholson, 2015). SCLC is associated with tobacco smoking, displaying a high mutational rate, and associated with loss-of-function mutations in important tumor suppressor genes TP53 and/or RB in the majority of the patients (Wistuba, Gazdar, & Minna, 2001). Similar to NSCLC, SCLC is also driven by the different oncogenic mutations. Around 20-40% of SCLC cases show activating mutations in the PI3K pathway, while 20 % exhibit amplification or upregulation of MYC family members, with around 9-10 % MYCL, 6% MYC or 4% MYCN (George et al., 2015; Mollaoglu et al., 2017; Semenova, Nagel, & Berns, 2015). Other known alterations include NOTCH, BCL2 and mutations in histone modifiers, such as CREBBP and EZH2 (Jiang, Sato, Kuwao, & Kameya, 1995; Semenova et al., 2015). Unfortunately, no targeted therapies are available for SCLC yet, the standard treatment for SCLC consists of radiotherapy and platinum-based chemotherapy, similar to KRAS-driven NSCLC, with nearly all patients relapse due to acquired resistance to chemotherapy (Alvarado-Luna & Morales-Espinosa, 2016; Wagner et al., 2018). When it comes to immune therapy, anti-PD-1/PD-L1 treatment have shown significant improvement in both lung cancer subtypes, with over 50% and 39% response in NSCLC and SCLC patients, respectively (Calles, Aguado, Sandoval, & Álvarez, 2019; Doroshow et al., 2019). These treatments have been approved for first line use in both NSCLC and SCLC. Nevertheless, more work is needed to improve treatments and diagnosis for lung cancer patients, as well as the development of new therapeutics to achieve better outcomes.

1.1.7 Acute myeloid leukemia

Due to the relevance to thesis work, I will also have a brief introduction about acute myeloid leukaemia (AML) in this section. AML is a type of haematological malignancy that arises in in the myeloid linage as immature progenitors resembling myeloblasts, which are unable to differentiate into functional blood cells. The accumulation of AML precursors in the blood system results in deficiencies in the production of several innate immune cell types, red blood cells and platelets. AML is a heterogeneous disease, consisting of several subtypes based on genetic and histopathological features. This includes AML with recurrent genetic abnormalities, therapy-related AML, myelodysplasia-related AML, AML with NPM1 mutation and AML with biallelic mutation of CEBPA, to name a few (Arber et al., 2016). The risk stratification of AML classifies patients into three main risk groups; favourable, intermediate, and adverse, based on their cytogenetics and molecular profile. AML is driven by many different oncogenic factors, including mutations in FMS-like tyrosine kinase 3 intracellular tyrosine kinase domain (FLT3-TKD), Runt-related transcription factor (RUNX1), DNA methyltransferase 3 alpha (DNMT3A), Ten-eleven translocation methylcytosine dioxygenase 2 (TET2), CCAAT/enhancer-binding protein alpha (CEBPA), nucleophosmin (NPM1), BCR-ABL1 fusion and mutant p53, many others (Döhner et al., 2017; Jones et al., 2010). MYC, which is a focus of this thesis, is also implicated in some

types of AML, as well as chronic myeloid leukemia (CML) and lymphomas. Examples of this are MYC deregulation in chromosome 8 trisomy in AML, or through the BCR/ABL translocation and activation in CML or indirectly as a consequence of activation of other oncogenic drivers, such as FLT3 (Jones et al., 2010; K. T. Kim et al., 2007; Sawyers, Callahan, & Witte, 1992). Moreover, MYC overexpression and deregulation in human leukaemia's is linked to poor prognosis and survival (Ohanian et al., 2019; Yun et al., 2019). These many different drivers of AML result in a heterogenous patients' profile, with different and variable responses to the treatments available.

The current long-term survival for AML is 40-45% in patients younger than 60 years and 20% for patients over the age of 60 (Tallman, Gilliland, & Rowe, 2005). Despite the heterogeneity in the molecular drivers of AML, the first standard treatment is usually an induction chemotherapy with general DNA synthesis inhibitors such as cytosine arabinoside (ara-C) and DNA-damaging agent anthracycline, with 60-70% complete remission in young patients, and 38-60% in older patients over the age of 70 (Döhner et al., 2017). This is followed by consolidation therapy, a second round of ara-C treatment, to eliminate remaining cancer cells. Patients with resistant AML subtypes, such as patients with p53 mutations, are treated with hypomethylating agents decitabine or aza-cytidine instead of ara-C and anthracycline (Quintás-Cardama et al., 2012). Following the consolidation therapy, patients might undergo bone marrow transplantation surgery (Popat et al., 2012). However, a few new targeted therapies have shown enhanced survival and specificity with lower toxicity in the past decade. For instance, FLT3 inhibitors, such as crenolanib and gilteritinib, have shown improved potency with considerably less toxicity compared to standard treatment (Döhner et al., 2017). Moreover, inhibition of SIRT1 protein expression in human FLT3-ITD AML LSCs has been proposed to improve treatment outcomes and remission in patients (L. Li et al., 2014). Additionally, IDH inhibitors, such as enasidenib, promoted differentiation, halted tumor proliferation and provided better complete remission rates, and were granted FDA approval for clinical use (Stein et al., 2019; Yen et al., 2017). Lastly, p53 reactivator, APR-246, has shown great promise in primary AML cells and currently in phase III clinical trials for the treatment of p53-mutated malignancies, including AML (Ali et al., 2016; Deneberg et al., 2016). These new therapies improve the quality of life for the patients and provide more robust and effective AML treatments, yet more advancement is needed.

1.2 Senescence

In this chapter of this thesis introduction, I will discuss cellular senescence, including mechanisms of senescence induction, its molecular features, its effect on the immune response and its potential as a therapeutic strategy against cancer.

1.2.1 Senescence induction and markers

Senescence is a state of permanent growth arrest, in which the cell does not respond to growth stimuli. It is a cellular process that is often triggered in response to different types of stress signals. Senescence was first described as a manifestation of cellular aging in a process called replicative senescence. In this case, cells undergo senescence due to the shortening of the telomeres, which are repetitive nucleotides sequences situated at the

ends of each chromosome. This shortening is a consequence of accumulative cellular growth cycles (Sfeir & de Lange, 2012) due to the inability of DNA polymerase to synthesize new DNA strand starting from the 3' end. Instead, RNA primers are used to initiate DNA replication of the lagging strand. These RNA primers are then degraded, resulting in the shortening of the DNA at the end of the chromosomes, eventually resulting in the erosion of the protective telomere caps at chromosomal ends. In addition, it can be triggered in response to many stimuli, other than telomere erosion, such as oncogene activation, oxidative stress, DNA damage and even as an effect of global relaxation of the chromatin, caused by histone deacetylase inhibitors and thereby block expansion of damaged cells (Munro, Barr, Ireland, Morrison, & Parkinson, 2004; Nakamura et al., 2008).

Senescence plays a role in cellular processes other than aging. Senescence has also been shown to play an important role in other processes in the life span of an organism, such as wound healing, regeneration and development. Studies in mouse models demonstrated that inhibition of senescence induction or the elimination of senescence cells delayed wound healing and increased the formation of fibrotic scars in the injured tissue (Demaria et al., 2014; Jun & Lau, 2010). It also has been shown that senescent cells suppress cell reprogramming during induced pluripotent stem cell generation by Yamanaka factors (OCT4, SOX2, c-MYC, and KLF4), indicating a role for senescent cells in regulating stemness (Hong et al., 2009). Additionally, senescence plays a role in embryogenesis, neurodegenerative diseases, diabetes and other cellular mechanisms and diseases. These observations demonstrate the importance of cellular senescence in different biological processes, ranging from aging, development, tissue repair to pluripotency. Here, I will focus on senescence induction via oncogene activation, a process called oncogene-induced senescence (OIS). In the past two decades, numerous studies have demonstrated that overexpression of oncogenes can trigger senescence. Early studies have revealed that overexpression of a mutant constitutively active form of HRAS induced senescence when introduced in normal cells (Serrano, Lin, McCurrach, Beach, & Lowe, 1997). Activation of RAS leads to replicative stress due to extensive cellular replication cycles and production of oxygen-reactive species (ROS). Later, KRAS, NRAS, $BRAF^{V600E}$, MYC, PAK4 and E2F overexpression were reported to trigger senescence *in vitro* and *in vivo* (Braig et al., 2005; Cammarano, Nekrasova, Noel, & Minden, 2005; Collado, Blasco, & Serrano, 2007; Dankort et al., 2007; Lazzerini Denchi, Attwooll, Pasini, & Helin, 2005; Michaloglou et al., 2005). Senescence induction has also been observed in response to genetic deletions of tumor suppressors, such as PTEN, von Hippel–Lindau (VHL) and neurofibromatosis type 1 (NF1), partly due to loss of normal regulation of cellular processes by these tumor suppressor protein pathways (Z. Chen et al., 2005; Courtois-Cox et al., 2006; Young et al., 2008). The stress signals generated from these events lead to induction of cellular senescence, thereby acting as a barrier against tumor development.

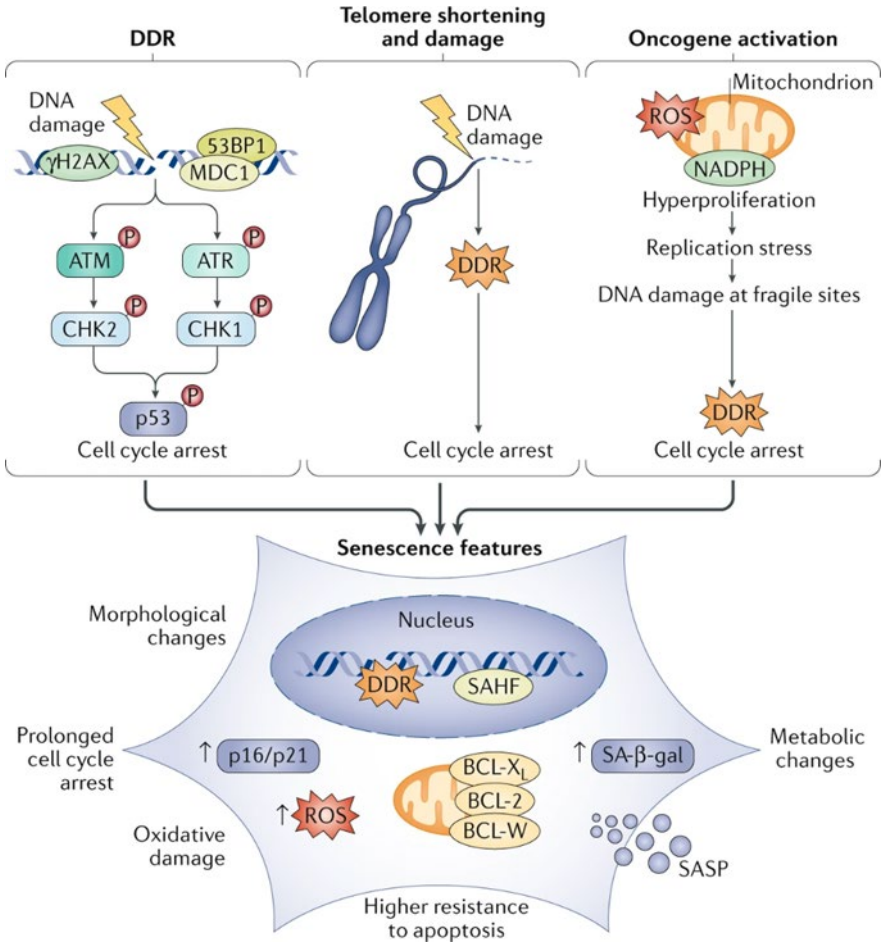

Figure 3: Different signals and pathways triggering senescence, and some characteristics of senescent cells. Adopted from Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. et al., Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol. 2021; 22:75-95.

While senescence can be triggered by many different stimuli, it is mainly induced via the activation of the following three main pathways; pRB/$p16^{INK4A}$, ARF/$p53/p21^{CIP1}$ and DNA damage response (Collado & Serrano, 2010; Larsson, 2011). For instance, cellular stress induced by oncogene activation, such as RAS, usually leads to the induction of the $p16^{INK4A}$ tumor suppressor protein (Serrano et al., 1997). $p16^{INK4A}$ blocks the CDK4/6-cyclin D complex, leading to the activation of pRB. Activated pRb binds and inhibits E2F, suppressing the transcription of its target genes, such as cyclin E1, by recruitment of DNA methyltransferases and histone deacetylases (Mason, Jackson, & Lin, 2004). Additionally, pRB triggers the degradation of SKP2 by E3 ligase complexes, leading to an increase in $p27^{KIP1}$ protein levels (Binné et al., 2007). These effects result in the termination of the cell cycle and impose a senescent state. p53-dependent senescence induction is triggered by another tumor suppressor protein encoded from the INK4A/CDKN2A locus, called ARF. Excessive signalling of oncogenes such as RAS triggers induction of ARF. The

accumulation of ARF leads to the phosphorylation of MDM2, which in turn liberates p53 from degradation and enhances its protein levels (Abida & Gu, 2008). p53 in turn activates the expression of $p21^{CIP1}$, resulting in the inhibition of CDK2, termination of DNA synthesis, and triggering senescence (Wierød et al., 2008). The third route of senescence induction is initiated through the DNA damage response. Sensor mechanisms within the cell detect DNA damage, a consequence of replicative stress and/or ROS production accumulated due to extensive growth signalling by oncogenes (Bartkova et al., 2006; Di Micco et al., 2006; Mallette, Gaumont-Leclerc, Huot, & Ferbeyre, 2007). DNA damage triggers the activation of two proteins involved in the DNA damage response mechanism, serine/threonine kinases ATM and ATR (J. Smith, Tho, Xu, & Gillespie, 2010). These biological sensors are activated in response to double-strand breaks and single-strand breaks, respectively. Once activated, ATM and ATR phosphorylate and activate their downstream effectors, Chk2 and Chk1. Chk2 phosphorylates and activates p53, leading to $p21^{CIP1}$ induction and senescence (Bartek & Lukas, 2007; Campisi, 2013; d'Adda di Fagagna, 2008).

Identification of senescent cells rely on the detection of different senescence markers. Senescent cells usually display high levels of β-galactosidase activity, which often referred to as senescence-associated β-gal (SA β-gal) activity, which is the most well-known marker of senescence. They also increase in size and become flattened, and often dense heterochromatin regions, termed Senescence-Associated Heterochromatin Foci (SAHF) appear in the nucleus (Narita et al., 2003). Other features of senescent cells include high metabolic activity, and as mentioned above induction of CDKIs, $p16^{INK4A}$ and $p21^{CIP1}$ and loss of proliferative markers, such as Ki-67 and depletion of nuclear lamina Lamin-B1 (LMNB1) (reviewed in (Hernandez-Segura, Nehme, & Demaria, 2018). But perhaps the most intriguing characteristic of senescent cells is the secretion of a variety of cytokines, chemokines, extracellular matrix modifiers and proteases, a process called senescence-associated secretory phenotype (SASP). This feature contributes to many different aspects of cancer, both negatively and positively, making it perhaps the most controversial characteristic of senescent cells, and therefore I will discuss this phenomenon in more detail below. Importantly, expression of various senescence markers is often context- and tissue-dependent, and all of these are not necessarily observed in all cells undergoing senescence. Worthy of note, some markers are also present in non-senescent cells during certain conditions, for instance, SA β-gal positive staining is not only exclusive for senescent cells, as some non-senescent cells can display high lysosomal activity. In addition, quiescent cells can display a reduction in proliferation markers and induction of CDKI expression. As a result, to determine if a cell is senescent, one cannot rely on a single marker, but needs to examine several of these markers.

1.2.2 Senescence-Associated Secretory Phenotype (SASP)

The SASP phenomenon is complex and is manifested by the secretion of a wide variety of growth factors, proteases and immune modulators, such as TGF-β, MMP3 and IL-6, that are involved in many cellular processes (Acosta et al., 2008; Kang et al., 2011). SASP is regulated at different levels; transcription of SASP genes is triggered by stresses such as DNA damage or oncogenic activation and mediated by the activation of p53 and pRB,

which in turn lead to the induction of p38 MAPK, NF-κB and CCAAT enhancer-binding protein β (C/EBPβ) among others factors (Freund, Patil, & Campisi, 2011). In addition to transcriptional regulation, p38MAPK enhances MAPK-activated protein kinase 2 (MK2) activity, leading to mRNA stabilization of different SASP components by heat shock protein 27 (HSP27) and AU-rich element RNA-binding protein 1 (AUF1) (Alspach et al., 2014). Moreover, mTOR stabilizes and protect MK2 from degradation, which enforces the SASP signalling in senescent cells (Herranz et al., 2015). Recent studies have also demonstrated that DNases are downregulated in senescent cells, allowing for the accumulation of cytosolic DNA fragments and triggering the activation of the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway (Glück et al., 2017; A. Takahashi et al., 2018). In turn, the cGAS–STING results in the activation of the NF-κB pathway, and subsequently, to SASP expression (Dou et al., 2017). Unlike NF-κB and C/EBPβ, it has been shown that NOTCH1 can prevent pro- inflammatory SASP cytokine secretion through induction of C/EBPβ degradation in senescent fibroblasts (Hoare et al., 2016). Finally, several epigenetic factors are also involved in SASP regulation. Studies in senescent human fibroblasts showed that inhibitors of histone deacetylase (HDAC) led to the activation of several SASP factors, even in the absence of DDR, suggesting a role for HDACs in suppressing SASP expression (Pazolli et al., 2012). Similarly, the chromatin modifier EZH2 has also been reported to suppress production of SASP (Ito, Teo, Evans, Neretti, & Sedivy, 2018). Although SASP is usually part of the senescence response, it is worth mentioning that the ectopic activation of $p16^{INK4A}$ or $p21^{CIP1}$ does not lead to SASP activation (Coppé et al., 2011). This observation shows that SASP induction is context-dependent and involves different mechanisms that are not fully understood yet.

Giving the large spectrum of factors that are part of the SASP, the effects resulting from this production are diverse and involve many pro- and anti-tumor aspects. For example, IL-6 secreted by senescent cells suppress tumor growth and maintain the senescent phenotype triggered by RAS induction (Kuilman et al., 2008). It has also been shown that IL-6 induces signal transducer and activator of transcription 3 (STAT3) expression in human fibroblasts, promoting reactive oxygen species (ROS) production and subsequently senescence induction in a paracrine manner (Nelson, Kucheryavenko, Wordsworth, & von Zglinicki, 2018). TGF-β and IL-1α can induce senescence in nearby cells, as well as reinforce senescence through a feedback loop mechanism (Acosta et al., 2013; Acosta et al., 2008; Orjalo, Bhaumik, Gengler, Scott, & Campisi, 2009). Additionally, chemokine (C–X–C motif) ligand 1 (CXCL1) and CXCL2 has been reported to enforce the senescent state in an autocrine manner (Acosta et al., 2008). More recently, Ruscetti et al. demonstrated that pro-angiogenic factors within SASP enhanced drug delivery and immune clearance of senescent cancer cells in a model of Pancreatic Ductal Adenocarcinoma (PDAC), potentially opening for new cancer treatment strategies utilizing SASP (Ruscetti et al., 2020). These are some of the observations suggesting a role of SASP components in halting tumorigenesis, but the SASP may also have pro-tumorigenic effects. For instance, IL-6 has been reported to contribute to tumor proliferation in breast, lung and prostate cancer models (Di et al., 2014; Hartman et al., 2013; Rojas et al., 2011; Song, Rawal, Nemeth, & Haura, 2011). Similarly, CXCL1 promoted proliferation in a model of esophageal tumors (B. Wang, Hendricks, Wamunyokoli, & Parker, 2006). Moreover, SASP has been implicated in epithelial-

mesenchymal transition (EMT) and metastasis. For instance, loss of hyaluronan and proteoglycan link protein 1 (HAPLN1) in aged fibroblasts was shown to promote tumor cell motility and metastasis (A. Kaur et al., 2019). Additionally, persistent SASP can induce endothelial cell proliferation and angiogenesis through VEGF secretion (Coppe et. al, 2006)(Oubaha, 2016). SASP may also contribute to epithelial-mesenchymal transition (EMT) and tumor invasion through the secretion of CXCL-1 and matrix metalloproteases 3 (MMP3) (Coppé, Kauser, Campisi, & Beauséjour, 2006; Laberge et al., 2012; D. Liu & Hornsby, 2007). In summary, SASP can have quite diverse and even contradicting effects on tumor cells and on tumor-promoting cells in the microenvironment. In addition, SASP contributes to different aspects of tumor immunity. In the rest of this chapter, we will discuss the different effects exerted by SASP on the immune system and how this potentially can be utilized for new treatments strategies.

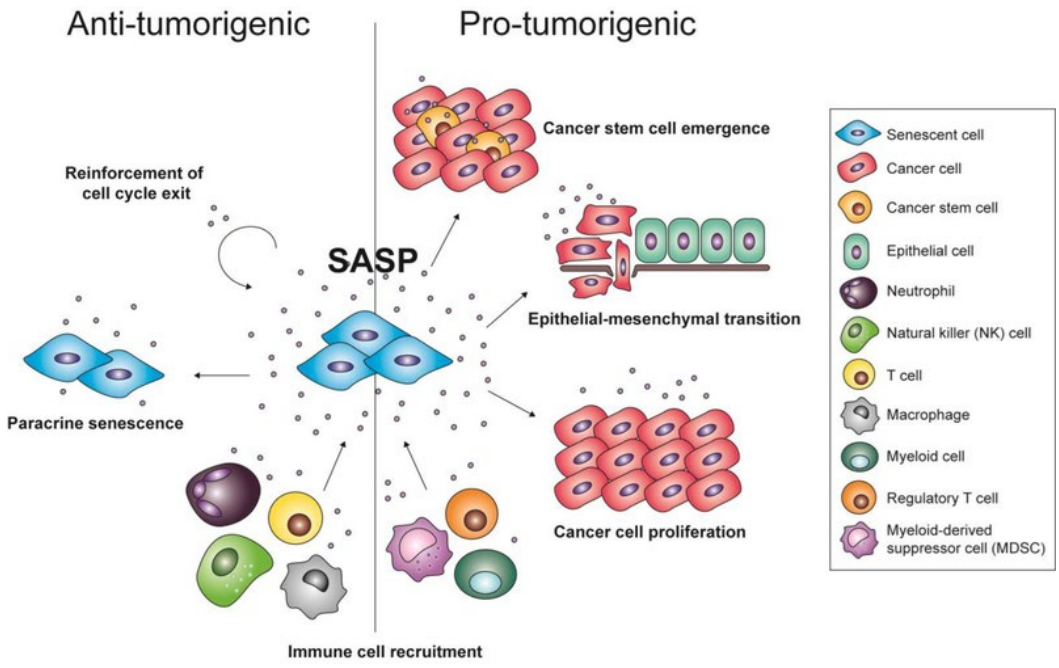

Figure 4: The pro- and anti-tumorigenic properties of the senescence-associated secretory phenotype (SASP). Adopted from Lau L, David G. et al., Pro-, and anti-tumorigenic functions of the senescence-associated secretory phenotype. Expert Opin Ther Targets. 2019; 23:1041-1051.

1.2.3 Senescence and Immunity

Besides cell cycle arrest, senescent cells engage in modulating the immune response in affected tissues. The immune modulatory effects are manifested by the changes in senescent cells as well as the secreted immune factors which are part of the SASP, which play different roles in regulating the immune response, positively as well as negatively. The different chemokines and cytokines secreted by the senescent cells create an immune inflammatory environment and results in the recruitment and activation of immune cells, such as macrophages, T cells and natural killer cells. Different studies have shown that

the recruitment of these immune cells can be beneficial. A study by Iannello et al. using a HRAS-driven hepatocarcinoma tumor model showed that the reintroduction of p53 led to senescence induction, elevated activation marker NKG2D expression on NK cells, infiltration of innate immune cells and tumor clearance (Iannello, Thompson, Ardolino, Lowe, & Raulet, 2013). NK cell recruitment and sensitization of senescent cells to NK cells killing has been reported by other studies. For instance, senescent cells can express UL16 binding protein 1 (ULBP1) and ULBP2, which can activate the cytotoxic function of NK cells (Textor et al., 2011). In addition, pharmacological induction of senescence by the CDK4/6 inhibitor palbociclib and the MEK inhibitor trametinib in a $KRAS^{G12D}$/p53-null lung cancer mouse model resulted in the induction of intercellular adhesion molecule-1 (ICAM-1), ULBP2 and MHC class I polypeptide-related sequence A (MICA) on tumors cells in a TNF-dependent manner (Ruscetti et al., 2018). These changes led to the recruitment of NK cells and reduction in the tumor mass. The ability of senescent cells to recruit NK cells is attributed to the secretion of SASP factors, such as CCL2, CCL5 and IL-15, highlighting some of the anti-tumor effects of SASP. The immune-modulatory effect of SASP factors extends also to other immune cells. SASP-mediated recruitment of immature myeloid cells and their subsequent differentiation into macrophages by CCL2 was reported in a $NRAS^{G12V}$-driven hepatocellular carcinoma model (Eggert et al., 2016). Similarly, senescence induction by p53 promoted M1-like macrophages differentiation and lead to tumor regression in another hepatocarcinoma mouse model (Lujambio et al., 2013). Furthermore, a study by Kang et al. demonstrated that SASP factors can facilitate anti-tumor immunity through the adaptive compartment of the immune system. Using the $NRAS^{G12V}$ liver cancer model, they showed infiltration of CD8 cytotoxic T cells and CD4 helper T cells into the senescent tumors in an ARF-independent manner, which led to clearance of senescent cells (Kang et al., 2011). However, the elimination of the tumor cells was mainly carried by cells of the innate immune cells, albeit this was dependent on the recruitment and activation of the T cell population.

Although SASP is involved in the recruitment of immune cells and tumor elimination, the response is context-dependent, and influenced the molecular makeup of the tumors as well as the tissue type. In the study by Eggert et al. mentioned above, it was shown that the transplantation of tumor cells into wildtype mice harbouring senescent hepatocytes led to fast tumor progression compared to transplanted mice lacking the senescent cells, suggesting that SASP factors secreted by the tumor cells suppressed the immune response. This involved CCL2-dependent recruitment of myeloid-derived suppressor cells (MDSCs) that blocked NK cell activation (Eggert, 2016). Another example of a heterogeneous SASP response is seen with CXCR2. CXCR2 was shown to inhibit proliferation and trigger senescence in KRAS-transformed fibroblasts, while it led to the recruitment of immune suppressive MDSCs in a RAS-driven PDAC model (Acosta et al., 2008(Steele et al., 2016). In addition, SASP-mediated immunomodulation was affected by p53 and PTEN status within the tumor population. For instance, the activation of NK cells by immune-related receptors induced on senescent cells, such as ULBP2, was lost upon p53 inactivation (Lujambio et al., 2013)(Iannello et al., 2013). Similar to p53 loss, PTEN-deficient senescent tumors were characterized by infiltrating MDSCs, resulting in immune suppression and tumor progression (Di et al., 2014;(Toso et al., 2014). This effect was shown to be dependent on JAK2/STAT3 signalling, as the inhibition of this pathway resulted in tumor regression and immune activation, uncovering an important role for

JAK2/STAT3 pathway in mitigating the immunomodulatory effect of SASP. Finally, SASP factors, such as VEGFA, can contribute to maturation of immune-inhibitory Treg cells, adding another possible mechanism in which SASP can stimulate pro-tumor immunity (Terme et al., 2013).

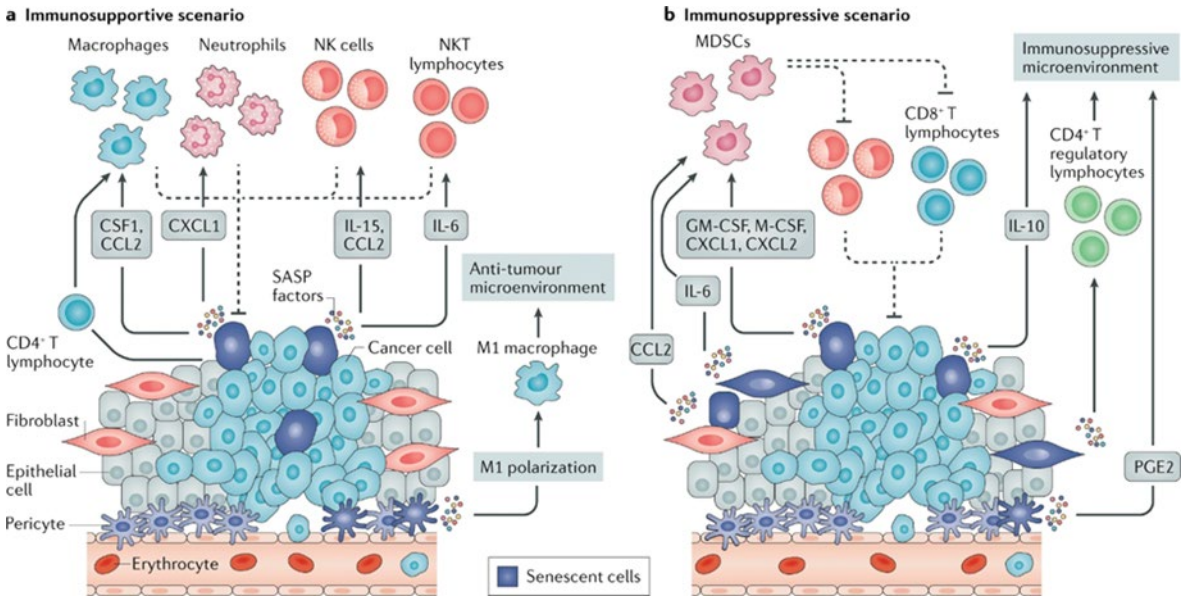

Figure 5: Different roles of SASP factors in tumor immune surveillance. a) Anti-tumor immune cell activation. b) Pro-tumor immune cell activation. Adopted from Faget DV, Ren Q, Stewart SA. Et al., Unmasking senescence: context-dependent effects of SASP in cancer. Nat Rev Cancer. 2019;19: 439-453.

These observations suggest that SASP can act as a double-edged sword, where in one hand it can contribute to immune activation and tumor elimination, and on the other hand to immunosuppression and tumor evasion. Nevertheless, this characteristic of senescent cells can possibly be exploited to combine immune therapy alongside senescence induction in tumor cells, an approach yet to be explored further.

1.2.4 Pro-senescence therapy

The ability to block tumor proliferation through senescence induction in different models has led to the idea of utilizing senescence as anti-cancer therapy – a concept known as pro-senescence therapy. This approach relies on the use of treatments that result in induction of senescence. An example of this are CDK4/6 inhibitors. As discussed in section 1.1.3, CDK4/6 has a crucial role in the inactivation of pRB and cell cycle progression, while its inhibition leads to withdrawal from the cell cycle and senescence induction. Several CDK4/6 inhibitors have been shown to induce senescence in different cancer cells. For instance, treatment with palbociclib resulted in senescence induction in melanoma, breast cancer and hepatocellular carcinoma among others (Bollard et al.,

2017; Goel et al., 2016; Yoshida, Lee, & Diehl, 2016), while abemaciclib induced senescence and blocked tumor development in xenografts of breast and lung cancer models (Gong et al., 2017; Torres-Guzmán et al., 2017). The successful use of senescence-inducing cell cycle inhibitors in several cancer clinical trials lead to FDA-approval for patient use of these drugs and paved the way for the possibility of pro-senescence therapy. Induction of senescence in cancer cells can also be achieved by targeting other senescence regulators. For example, DNA methyltransferases (DNMTs), such as 5-Aza-2-deoxycytidine (5-aza), and HDAC inhibitors, such as suberoylanilide hydroxamic acid (Vorinostat), have been shown to disturb tumor proliferation and induce senescence in different cancer cell lines, including MCF7 (breast cancer), U2OS (osteosarcoma), HCT116 (colon cancer) as well as in T cell lymphoma patients (Almeida et al., 2017; Putri, Widodo, Sakamoto, Kaul, & Wadhwa, 2017; Xu, Perez, Ngo, Gui, & Marks, 2005). The induction of senescence by these drugs is possibly due to loss of promoter hypermethylation and induction of $p16^{INK4A}$ and activation of the DDR signalling. Similarly, p53 reactivating drugs can be used in a pro-senescence therapy strategy (Iannello et al., 2013; Xue et al., 2007).

Another aspect of the pro-senescence therapy is the secreted SASP factor's abilities to induce remodelling of the microenvironment and anti-tumor immunity. This feature of SASP was demonstrated in many systems, which we mentioned in the previous section. SASP can promote vascular normalization in the tumor area, enhancing anticancer drug delivery and immune cell infiltration to the tumor area (Ruscetti et al., 2020). Activation of NK cells against senescent tumor cells in different settings was achieved by the re-activation of p53, pharmacological inhibition of cell cycle regulators or activation of DDR by DNA-damaging agents, such doxorubicin (Iannello et al., 2013; Ruscetti et al., 2018; Soriani et al., 2009). Anti-tumor M1-like macrophages can also contribute to pro-senescence therapy response and clear senescent cells from tissues (Lujambio et al., 2013). Other immune cells triggered by SASP include adaptive immune cells, such as T cells, which can be part of this therapeutic approach. In addition to the recruitment of CD8 cytotoxic and CD4 helper T cells demonstrated in the hepatocellular carcinoma model by Kang et al., the dual pharmacological blockade of MDM2 and AURKA in a B16F0 melanoma model induced cellular senescence in the tumor cells, accompanied by CCL5 secretion (Vilgelm et al., 2015). Re-activation of senescence by this treatment was characterized by recruitment of T cells, as well as other leukocytes, into the tumor area and aided in tumor clearance.

The immunomodulatory effects of SASP have also been used in combination with immunotherapies to achieve eradication of cancer cells. In addition to the recruitment of immune cells by SASP, senescence induction can possibly sensitize 'immunologically cold' cancers to immune therapy, as in the case of the induction of ULBP1 & 2 expression in senescent cells mentioned in the previous section. For instance, a study by Vilglem et al. showed a robust killing of tumor cells by activated TILs following senescence induction through AURKA inhibition in melanoma cells (Vilgelm et al., 2016). This enhanced TIL killing efficacy was dependent on CCL5 as part of the SASP secretome. The immune enhancing properties of pro-senescence therapy were also observed in other studies, utilizing checkpoint inhibitor immunotherapies, further supporting the approach of combining pro-senescence and immune therapies (Hu-Lieskovan et al., 2015)Goel et

al., 2017). However, SASP can also have pro-tumor tumors effects by blocking anti-tumor immunity. To counter this, new strategies has been proposed to try to modulate the SASP response to inhibit its pro-tumor components. As an example, the use of docetaxel, a mitotic spindle inhibitor, together with a CXCR2 antagonist was shown to induce senescence in PTEN-null mouse prostate tumour cells while abrogating CXCR2-driven Gr-1+ MDSC infiltration *in vivo* (Di Mitri et al., 2014). Inhibiting the SASP-regulatory JAK2/STAT3 pathway was also evaluated in this model. Docetaxel treatment in combination with pharmacological inhibition of JAK2 by NVP-BSK805 led to the attenuation of the SASP immunosuppressive signalling and enhanced the recruitment of T, NK and B cells into the tumor, resulting in tumor regression (Toso et al., 2014). The modulation of the SASP response in these studies while retaining the cell cycle arrest, provided a proof of concept that targeting certain SASP regulators, such as NF-κB, p38/MAPK, HDACs and SASP factors like IL-1 and IL-6 enhance the pro-senescence therapy outcome.

Aside from SASP modulation, the prospect of targeted elimination of senescent cells by pharmacological inhibitors targeting vulnerabilities in senescent cells is emerging as a promising strategy in cancer treatments. This idea emerged after studies have demonstrated that senescent cells can be targeted and removed (Y. Zhu et al., 2015). Chang et al. subsequently demonstrated the senolytic ability of the pan-BCL2 inhibitor ABT-263 (Navitoclax) in mouse models used for aging studies (Chang et al., 2016). Since then, navitoclax has been used in many cancer studies, including breast cancer, ovarian cancer and small lung cancer, showing promising results for apoptosis induction and eradication of senescent cancer cells (Fleury et al., 2019; Nakajima et al., 2016). A recent study by Galiana et al. demonstrated that the treatment with navitoclax, encapsulated in targeted nanoparticles, following senescence induction by palbociclib resulted in reduction of metastases, inhibition of tumor growth, with minimal toxicity in a triple negative breast cancer (Galiana et al., 2020). This work further demonstrates the potential of this strategy in combating cancer through pre-senescence therapy. Other BCL-2 inhibitors, such as obtoclax, showed similar effects as navitoclax when combined with the bromodomain and extraterminal motif (BET) inhibitor JQ1 in breast cancer (Gayle et al., 2019). The senolytic effect was not restricted to anti-apoptotic inhibitors; elimination of senescent cells has been achieved using mTOR inhibitors, DNA replication inhibitors as well as using HDAC inhibitors in different cancer models (Demaria et al., 2017; Samaraweera, Adomako, Rodriguez-Gabin, & McDaid, 2017; C. Wang et al., 2019). Additionally, targeting proteins and enzymes involved in metabolism, exploiting the high metabolic activity of senescent cells, have led to synthetic lethal effects and elimination of senescent cells (Dörr et al., 2013; Kaplon et al., 2013; Wiley & Campisi, 2016). The list of senolytic drugs also extends to non-cancer treatments and natural active compounds, such as type 2 diabetes drug metformin and fisetin, which have the ability to induce cytotoxic effects in senescent cells (Moiseeva et al., 2013; Yousefzadeh et al., 2018). Finally, another demonstration of the potential of combining pro-senescence therapy with immunotherapies to achieve a senolytic effect was demonstrated in a recent publication from Scott Lowe's lab. Utilizing urokinase-type plasminogen activator receptor (uPAR), a cell-surface protein that is expressed on senescent cells after palbocicilb and trametininb combination treatment, they showed that injection of anti-uPAR CAR T cells led to

elimination of senescent tumor cells in a lung adenocarcinoma mouse model (Amor et al., 2020).

The different approaches of utilizing pro-senescence therapy discussed above can potentially be implemented for a new, more effective cancer therapy strategies in the future. However, like other cancer therapies used in the clinic, pro-senescence therapy faces hurdles that need to be overcome. For instance, the response to senolytic drugs varies between different senescent cells in different tissues and does not always result in an effective clearance of senescent cells. In addition, senescence is required for other cellular processes, such as wound healing, which warrant its use with precaution. Nevertheless, pro-senescence therapy has a promising potential as a combination cancer treatment with immunotherapy in the clinic in the future.

1.3 The MYC oncoprotein

In the final part of this introduction, we will be going through the role of one of the most frequently deregulated oncoproteins, MYC, which is in the centre of this thesis. MYC was one of the first oncogenes to be identified (Duesberg & Vogt, 1979; Hu, Lai, & Vogt, 1979; Sheiness & Bishop, 1979). It plays an important role in many cellular processes, including cell proliferation, apoptosis, cell growth and metabolism, which place it at the heart of many hallmarks that are pivotal in tumorigenesis. As such, understanding MYC biology and functions can provide valuable knowledge that can be utilized to improve current cancer treatments and develop new and more robust therapeutic approaches to combat cancer. During this chapter, I will go in more detail through MYC functions and regulation of relevance to this thesis work.

1.3.1 MYC functions

The *MYC* gene, also known as c-*MYC*, belongs to the MYC family of proteins that also includes N-MYC and L-MYC, with MYC being the most commonly expressed family member in different tissues. The *MYC* gene encodes a transcription factor containing a basic region/helix-loop-helix/leucine zipper (bHLHZip) domain and a transactivation domain at the C- and N-terminus, respectively. MYC also contains several highly conserved regions called MYC boxes (MB0, MBI, II, IIIa, IIIb and IV) located in its transactivation domain and central region, and which are essential for MYC's function in transcriptional activation and repression, as well as for its own regulation by other factors (Farrell et al., 2014; Kato, Barrett, Villa-Garcia, & Dang, 1990; Murre, McCaw, & Baltimore, 1989). The MYC boxes are found in all the MYC family proteins, except for the absence of MBIIIb in L-MYC.

MYC regulates the transcription of a variety of genes involved in the cellular processes under its control. To achieve this, MYC needs to form heterodimers with the bHLHZip protein MAX through the bHLHZip domains of the two proteins. This is crucial for most of MYC's functions (Blackwood & Eisenman 1991) (Mathsyaraja et al., 2019). The MYC:MAX heterodimer binds specifically to DNA sequences called E-boxes situated in promoter and enhancer regions of target genes. The MYC-type E-boxes are composed of

the canonical CACGTG or related sequences (Blackwood & Eisenman, 1991). MYC recruits different cofactors to promoters, such as histone acetyl transferase (HAT) complexes containing TRAPP or p300/CBP, as well as transcription elongation factor b (P-TEFb), and stimulate initiation, pause release and elongation of transcription from its target genes (Kress, Sabò, & Amati, 2015; Tu et al., 2015). This ability of the MYC:MAX heterodimer and associated co-factors to regulate transcription allows MYC to orchestrate multiple processes in the cell, such as cellular proliferation, apoptosis, protein synthesis and metabolism. MYC regulates several genes involved in the cell cycle that will be described further below. Moreover, MYC activation triggers protein synthesis, through the activation of transcription of ribosomal RNA, ribosomal proteins and 5S and tRNAs through RNA Pol I, II and III, respectively (Arabi et al., 2005; Gomez-Roman, Grandori, Eisenman, & White, 2003; Grandori et al., 2005; Schlosser et al., 2003). MYC also contribute to mRNA translation and protein synthesis by the regulation of CAP-dependent translation initiation factors, such as eukaryotic translation initiation factor 4E (eIF4E) (Schmidt, 2004). Further, MYC plays an important role in cellular metabolism regulation and energy production, which is frequently deregulated in cancer. For instance, it has been shown that MYC activates lactate dehydrogenase A (LDHA) expression, an enzyme important in glycolysis, as well as the induction of glutamate metabolism and glycolysis by suppressing its negative regulator, miR-23a/b, and deregulating glucose transporter 1 (GLUT1) in cancer cells (Gao et al., 2009; Osthus et al., 2000; Shim et al., 1997). In addition, MYC promotes glycolysis through the induction of pyruvate kinase M2 (PKM2) and monocarboxylate transporter 1 (MCT1) (Dang, 2013; Stine, Walton, Altman, Hsieh, & Dang, 2015). The high metabolism rate accompanying MYC, in turn leads to the production and accumulation of reactive-oxygen species (ROS), which leads to DNA damage and genomic instability, an important characteristic often exhibited by tumor cells (Egler et al., 2005). Additionally, MYC is known to induce DNA damage via replication stress, as a result of elevated replication-fork collapse in hyper-proliferative cells (Gorgoulis et al., 2005; Srinivasan, Dominguez-Sola, Wang, Hyrien, & Gautier, 2013). This can induce apoptosis or senescence, which will be discussed further below.

On the other hand, MYC can also repress the expression of certain genes by cooperating with MIZ-1, a zinc finger transcription factor involved in both activation and repression of transcription (Peukert et al., 1997; Staller et al., 2001; van Riggelen et al., 2010). The MYC:MIZ1 complex represses transcription through the recruitment of DNA methyl transferases, which leads to the hypermethylation and the transcriptional inactivation of target genes (Licchesi et al., 2010). An important example of this mechanism is the silencing of the $p21^{CIP1}$ gene promoters via MYC:MIZ1 and DNMT3a (Brenner et al., 2005). In addition, MYC is also suggested to repress transcription indirectly through the induction of PTEN, resulting in the activation of EZH2, which modifies chromatin structure by histone 3 lysine 27 trimethylation ($H3K27me^3$), and thereby repressing genes indirectly (M. Kaur & Cole, 2013). With its wide effect on transcription, MYC's mode of action in transcriptional activation is controversial and an area of discussion. A study by Lin and colleagues suggested that MYC acts as a universal amplifier of gene transcription, and as such does not regulate specific target genes. This view was opposed by work from Amati and colleagues, indicating that MYC drives expression of specific sets of target genes, and therefore does not act as a global transcriptional amplifier (C. Y. Lin et al., 2012; Nie et al., 2012; Sabò et al., 2014). This standpoint was further supported

by Walz et al. work, suggesting that MYC regulates distinct classes of target genes, either positively or negatively (Walz et al., 2014). However, both sides in this debate seem to agree that MYC activation, directly or indirectly has global effects on transcription.

1.3.2 Regulation of MYC expression

MYC expression is controlled on different levels, from transcription to protein turn over, and involves many feedback loops and regulators. At the transcription level, MYC expression is triggered by several mitogenic signalling pathways driving cellular proliferation, such as the RAS, MAPK, WNT/β- catenin and JAK/STAT pathways and can also be repressed by anti-growth signalling, such as the TGFβ and interferon pathways (C. R. Chen, Kang, Siegel, & Massagué, 2002; He et al., 1998; Kiuchi et al., 1999; Sears et al., 2000). This regulation often involves super-enhancers found at distant upstream or downstream regions from the MYC loci, which act at the promoters from long distances (Cao et al., 2017; Schuijers et al., 2018). These signalling pathways and regulators ensure timely expression of MYC under different conditions, and the deregulation of these pathways, which is often observed in cancer, is one of the mechanisms leading to aberrant MYC expression during tumorigenesis. In addition, MYC mRNA translation is tightly regulated by the mTOR/eIF4F pathway (Csibi et al., 2014; Kress et al., 2011; Notari et al., 2006; Wall et al., 2008). mTOR phosphorylates the eIF4E-bound 4E-BP, which results in the dissociation eIF4E, which proceeds to interact and form a complex with other eIF4 proteins. The eIF4F complex recruits eIF4A to the mRNA, unwinding of the secondary structure of its 5' UTR, which in turn kick start the ribosomal translation of the MYC mRNA (Bhat et al., 2015; Roux & Topisirovic, 2018; Wiegering et al., 2015; Wolfe et al., 2014).

In addition, MYC is a target for various posttranslational modifications affecting its function and stability. Early studies have shown that MYC is subjected to regulation by phosphorylation, mainly on its threonine 58 (Thr-58) and serine 62 (Ser-62) residues. Phosphorylation of MYC at the Ser-62 residue is for instance mediated by the ERK kinase, which was reported to enhance MYC protein stability (Lutterbach & Hann, 1994; Sears et al., 2000). The phosphorylation of MYC at Ser-62 plays multiple roles in its regulation and function and can also be carried by other kinases, including CDK1, CDK2 and CDK5, and serves to activate MYC and its transcriptional activity (Hoang et al., 1995; Hydbring et al., 2010; Seo, Kim, Bae, Soh, & Lee, 2008). This phosphorylation also serves as a priming event for further MYC phosphorylation by GSK3β, which phosphorylates MYC at Thr-58 residue. This ultimately results in MYC protein degradation (Gregory, Qi, & Hann, 2003; Lutterbach & Hann, 1994). Thr-58/Ser-62-phosphorylated MYC attracts the F-box protein FBXW7 (Welcker et al., 2004), which is the substrate-binding subunit of the multi-subunit SCF (SKP1-CULLIN-F-box) E3 ligase complex. The SCF^{FBXW7} E3 ligase complex binds and poly-ubiquitylates MYC, thereby targeting it for proteasomal degradation (Gregory & Hann, 2000; Salghetti, Kim, & Tansey, 1999; Yada et al., 2004). The efficiency of FBXW7-mediated MYC degradation is reported to be dependent on prior protein phosphatase 2A (PP2A) activity. PP2A binds Thr-58/Ser-62 phosphorylated MYC and dephosphorylates Ser-62 with the help of Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1), facilitating subsequent MYC degradation (Yeh et al., 2004). Moreover, de-phosphorylation of MYC Ser-62 by PP2A was shown to be inhibited by

the protein Cancerous Inhibitor of PP2A (CIP2A), leading to MYC stabilization, which was shown to take place at the nuclear lamina (Junttila et al., 2007; Myant et al., 2015).

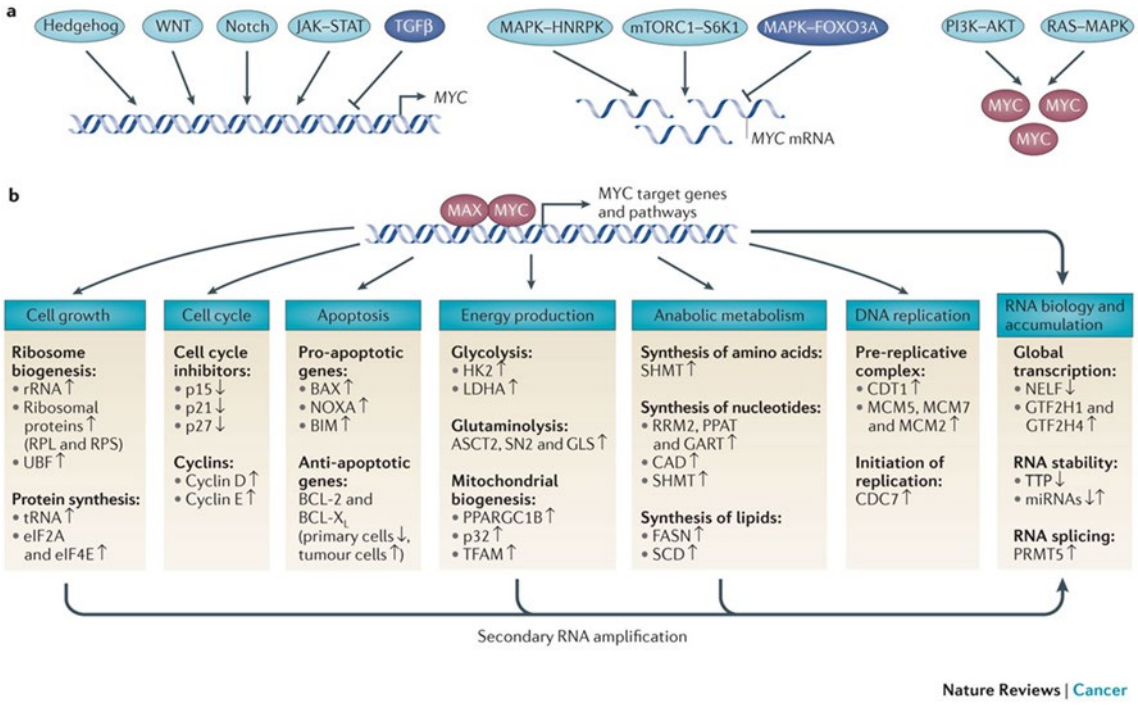

Figure 6: Regulation and function of MYC. The MYC proto-oncogene is regulated by major growth-regulatory and oncogenic signalling pathways. Overview of the different cellular processes and targets regulated by MYC. Adopted from. Kress TR, Sabò A, Amati B. et al., MYC: connecting selective transcriptional control to global RNA production. Nat Rev Cancer. 2015;15:5 93-607.

Interestingly, RAS induction results in the inactivation of GSK3β via the PI3K/AKT pathway, leading to the enhancement of MYC protein stability (Kumar, Marqués, & Carrera, 2006). In addition to FBXW7, a number of other E3 ligases also regulate MYC. Previous work by our and Bill Tansey's groups have shown that the F-box protein SKP2 also interacts with and ubiquitylate MYC, promoting its proteasomal degradation (S. Y. Kim, Herbst, Tworkowski, Salghetti, & Tansey, 2003; von der Lehr et al., 2003). Interestingly, and in contrast to FBXW7, ubiquitylation and degradation of MYC by SKP2 also enhanced MYC-driven transcription. Moreover, it was reported recently that the HECT E3 ligase, UBR5 is directly involved in the ubiquitination and degradation of the MYC protein (Schukur et al., 2020). Further, work from our group, demonstrated that interferon-γ (IFN-γ)-induced $p27^{KIP1}$ promoted MYC proteasomal degradation through direct $p27^{KIP1}$ binding, engaging an unknown E3 ligase (Bahram et al., 2016). Ubiquitylation of MYC by E3 ligases is not always resulting in MYC degradation. For instance, poly-ubiquitylation of MYC by HUWE1/HECTH9 or FBXO28 leads to the recruitment of acetylation complexes such as TRAP and p300/CBP, enhancing MYC's transcription activation function (McMahon, Van Buskirk, Dugan, Copeland, & Cole, 1998; K. Zhang, Faiola, & Martinez, 2005). In addition, E3 ligase β-TRCP has been

shown to stabilize the MYC protein by inducing poly-ubiquitination via the UbcH5 ubiquitin-conjugating enzyme, antagonizing Fbw7-mediated ubiquitination (Popov, Schülein, Jaenicke, & Eilers, 2010).

1.3.3 MYC in cancer

The MYC protein is deregulated in over half of human cancers and is often associated with poor prognosis (Stine et al., 2015). In fact, MYC is the most frequently amplified oncogene in human cancer (Beroukhim et al., 2010), ranging from over 30% of ovarian cancer, 21% of breast cancer and 14% of pancreatic adenocarcinomas, among others (Bailey et al., 2016; C. G. A. R. Network, 2011). Amplification of the other members of the MYC family, such as MYCN and MYCL is also observed in human cancers, such as neuroblastoma and small cell lung carcinoma (C. G. A. Network, 2012; Pugh et al., 2013). Gene amplification is not the only form of MYC aberration observed in cancer. Chromosomal translocation leading to MYC deregulation is observed in Burkitt's lymphoma and multiple myeloma, in which the MYC locus is placed in the vicinity of the highly active immunoglobulin enhancers (Finver et al., 1988; Jiménez et al., 2017). In addition to the chromosomal aberrations mentioned above, MYC deregulation in cancer cells can also be caused by deregulated expression due to genetic or epigenetic aberrations affecting super-enhancers controlling the MYC loci observed in T cell leukaemia's for instance, or indirectly through the constitutive activation of pathways upstream of MYC, such as the MAPK and WNT pathways observed in different tumor types (Hnisz et al., 2013; Myant & Sansom, 2011; Romeo et al., 2015; Sears, Leone, DeGregori, & Nevins, 1999; J. Zhu, Blenis, & Yuan, 2008) (Bellahcène, Castronovo, Ogbureke, Fisher, & Fedarko, 2008; Chan et al., 2010). Other mechanism of MYC de-regulation in cancer is through the stabilization of MYC protein level. An example of this is the loss of FBXW7, a regulator of MYC protein turnover, which results in the stabilization and subsequent deregulation of the MYC protein (Davis, Welcker, & Clurman, 2014). GSK3β inactivation, by the RAS/PI3K/AKT pathway for instance, is another mechanism that is frequently observed in cancer cells to deregulate the MYC protein, which also results in blocking GSK3β phosphorylation of MYC at Thr-58 and preventing MYC degradation (Manning & Toker, 2017; Sears et al., 2000). Another mechanism observed in Burkitt's lymphoma is mutations in MYC Thr58, which plays an important role in regulating MYC protein stability, resulting in a substantial reduction of proteasome-mediated degradation and ubiquitination, leading to MYC deregulation (Bahram, von der Lehr, Cetinkaya, & Larsson, 2000; Salghetti et al., 1999). Moreover, the overexpression of CIP2A in different types of cancers, which inhibit Ser-62 phosphorylation by PP2A and protect MYC from proteasomal degradation (Khanna, Pimanda, & Westermarck, 2013).The dependency on MYC for sustained tumor growth has been highlighted in many studies. For instance, *in vivo* studies in mice elegantly demonstrated tumor regression upon MYC inactivation for many types of tumors, such as T cell lymphoma, acute myeloid leukemia and pancreatic cancer mouse models (Arvanitis & Felsher, 2005; Felsher & Bishop, 1999; Jonkers & Berns, 2004; Pelengaris, Khan, & Evan, 2002). These studies utilized the conditional tetracycline-induced system (Tet-on/Tet-off) or the conditional tamoxifen-induced system to activate and deactivate MYC expression at will *in vivo*. In the tetracycline induced system, the expression of the gene of interest, which is placed under the tetracycline response element (TRE) promoter,

is either activated (on) or deactivated (off) by the tetracycline transactivator protein (tTA). The tTA protein activity requires tetracycline, or its derivatives such as doxycycline, to

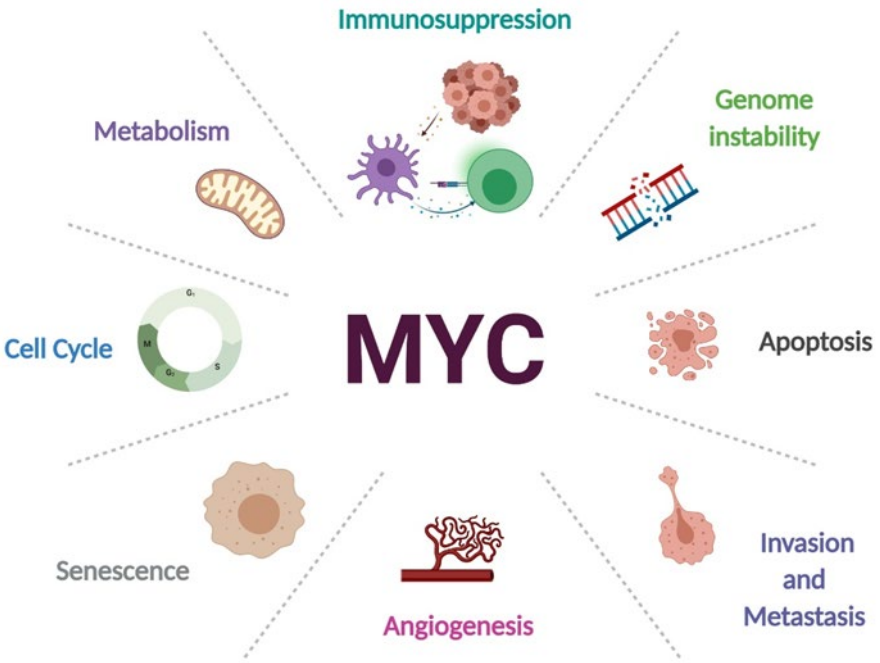

Figure 7: Role of MYC in cancer development. MYC is involved in many different processes governing tumor development. Created with BioRender.com.

activate/deactivate the expression of the gene of interest. In the tamoxifen-induced system, the protein of interest is fused to a modified human-estrogen ligand-binding domain (ER), where the activity of the ER-fused protein is triggered by 4-hydroxytamoxifen/tamoxifen. In these studies, turning off MYC expression in established tumors, by the withdrawal of doxycycline or tamoxifen, induced apoptosis and tumor regression, highlighting tumor dependency on MYC. This observation gave rise to the theory of 'oncogene addiction', where cancer cells become highly dependent on the expression of certain oncogenes for their survival. Another demonstration of MYC's importance in tumor progression was provided by a work by Gerald Evan, Laura Soucek and colleagues. In their studies, an inducible dominant negative form of MYC, termed Omomyc, was able to block tumor formation and induce tumor regression in a KRAS-driven lung tumor model, which was only overcome by silencing of Omomyc selected for in a small subset of tumors cells (Soucek et al., 2008; Soucek et al., 2013). The Omomyc approach was further evaluated in many different cancer models, including invasive astrocytoma, WNT-driven breast cancer model, patient-derived glioblastoma xenografts and PDAC mouse model. The results from these studies demonstrated that the tumors were dependent on (or "addicted to") MYC to maintain tumor proliferation, progression and for remodelling of the micro-environment (Alimova et al., 2019; Annibali et al., 2014; Beaulieu et al., 2019; Galardi et al., 2016). Similarly, a study from Sansom et al. using a model of adenomatous

polyposis coli (APC)-deficient colorectal cancers, which is characterised with deregulated WNT/ β-catenin pathway, demonstrated that WNT-driven MYC expression is required for the molecular and pathological phenotypes associated with tumor progression (Sansom et al., 2007).

MYC is clearly essential for many cellular processes during cancer development. Different studies provide evidence that MYC expression is required for a proper execution of angiogenesis during tumorigenesis through regulation of VEGF, HIF-1α and other angiogenic factors (Baudino et al., 2002; C. W. Chen, Yeh, Shiau, Chiang, & Lu, 2013). MYC has also been proposed to play a role epithelial-to-mesenchymal transition (EMT). This process is often driven by TGF-β and its downstream transcription factor SNAIL. Studies have demonstrated that MYC can activate SNAIL through regulating several micro-RNA clusters targeting SNAIL (A. P. Smith et al., 2009). Additionally, MYC also seems to play a role in cell invasion, migration, and metastasis, although this is controversial. A pro-metastatic role for MYC was proposed based on its regulation of proteins required for cytoskeleton regulation and remodelling, such as OPN, LGALS1 and RHOA, which also plays a role in migration, cell invasion and EMT (Chan et al., 2010; C. Martinez, Churchman, Freeman, & Ilyas, 2010; T. Wang et al., 2019; Yan et al., 2009). On the other hand, work from Bishop lab and others rather suggested that MYC does not induce invasion and metastasis using a primary keratinocytes model, as well as breast cancer models, and instead downregulated the expression of α and β integrins involved in invasion and metastasis (Gebhardt et al., 2006; H. Liu et al., 2012; Welm, Kim, Welm, & Bishop, 2005). Another report has also suggested that MYC expression dramatically blocked tumor invasion and cell migration in. human lung adenocarcinoma cells and drosophila models (Ma et al., 2017). Further studies are required to determine whether MYC promotes invasion and metastasis or not, and whether this might be context dependent. Taken together, the studies above emphasize the important role of MYC in different aspects of the tumorigenesis, and during the rest of this chapter, I will focus on certain characteristics of MYC that are particularly relevant to this thesis work.

1.3.4 MYC and the cell cycle

One of the prominent roles of MYC is its effect in promoting cell cycle and proliferation. Following mitogenic signalling, MYC levels increase dramatically and aid in facilitating the progression during the different stages of the cell cycle by regulating expression of different proteins involved in this process. For instance, it has been shown that MYC induces the expression of cyclin D2 and CDK4, which together form a complex that phosphorylates and inactivates RB during late G1 phase of the cell cycle (Hermeking et al., 2000). Additionally, MYC contributes to upregulation of cyclin E1 and cyclin E3 expression, required for CDK2 function during cell cycle progression (Bouchard et al., 1999; Steiner et al., 1995) (Steiner, 1995). MYC's effect on cell cycle extends to the promotion of G2/M phase transition through the induction of cyclin B expression, and subsequently enhancing the formation of cyclin B/CDK1 complexes required for M phase entry (Yin et al., 2001). Aside from induction of CDKs and cyclins, MYC also promotes the cell cycle by regulating CKIs involved in blocking cell cycle progression. For example, MYC causes sequestering of $p27^{KIP1}$ via induction of CDK4/6-cyclin D complexes, which bind $p27^{KIP1}$, thereby freeing CDK2-cyclin E from inhibition by $p27^{KIP1}$ and resulting in

the hyperphosphorylation of RB and the transition to S phase (Pérez-Roger, Solomon, Sewing, & Land, 1997). Furthermore, MYC suppresses $p27^{KIP1}$ levels through different mechanisms. At the mRNA level, MYC represses $p27^{KIP1}$ expression either directly by inhibiting Forkhead box O proteins FOXO3a from activating the p27 promoter or through miRNA-222 and miRNA-221 targeting p27 mRNA (Chandramohan et al., 2008; J. W. Kim, Mori, & Nevins, 2010; W. Yang et al., 2001). Additionally, MYC enhances expression of components of the SCF^{SKP2} E3 ubiquitin ligase complex, which recognize $p27^{KIP1}$ after phosphorylation by the CDK2-cyclin E complex, leading to $p27^{KIP1}$ubiquitylation and proteasome-mediated destruction (Bretones et al., 2011; Montagnoli et al., 1999). The expression of the CDK inhibitors $p15^{INK4b}$ and $p21^{CIP1}$ are also repressed by MYC together with MIZ-1 (Staller et al., 2001; Wu et al., 2003). At high MYC levels, MYC binds MIZ1 and recruits the DNA methyltransferase DNMT3a to $p15^{INK4b}$ and $p21^{CIP1}$ gene promoters, leading to the subsequent methylation and inactivation these genes (Brenner et al., 2005; Staller et al., 2001). $p15^{INK4b}$ is known to bind to and inhibit CDK4/6 following its induction by the TGF-β pathway, thereby blocking the cell cycle progression and inducing cell cycle arrest (Sherr & Roberts, 1995). $p21^{CIP1}$ blocks cell cycle progression by binding to and inhibiting CDK2-cyclin E and CDK2-cyclin A, which are active during late G1 and S phases of the cell cycle (Gartel, 2005). $p21^{CIP1}$ is also reported to regulate DNA synthesis and DNA damage repair in association with proliferating cell nuclear antigen (PCNA) (Waga, Hannon, Beach, & Stillman, 1994; Xiong, Zhang, & Beach, 1992). MYC has also been reported to play a role in DNA replication. It induces the expression of proteins important for replication, such as Cell Division Cycle 6 (CDC6), origin complex recognition complex (OCR) and minichromosomal maintenance proteins (MCMs), proteins required for replication initiation and elongation during DNA replication (Fernandez et al., 2003; Zeller et al., 2006). In addition, MYC promotes nucleotide production, thereby further contributing to replication and DNA synthesis (Mannava et al., 2008). Furthermore, MYC also triggers expression of components of the APC/C protein complex, an important factor regulating the destruction of securin and cyclin B1, which is a perquisite for induction of anaphase (Primorac & Musacchio, 2013). Moreover, MYC also plays a role in maintaining telomeres through the induction of hEST2 expression and upregulating expression of the telomerase subunit hTERT, which is limiting in adult cells, and one of the key features in tumor development (J. Wang, Xie, Allan, Beach, & Hannon, 1998). Finally, MYC is involved in senescence regulation, which we will be revisited in the next section. These many different contributions of MYC to cell cycle progression place it at the heart of cancer development.

1.3.5 MYC in apoptosis and senescence

In addition to its well-documented role in promoting cellular proliferation and growth, high MYC expression triggers apoptosis both through the intrinsic and extrinsic apoptotic pathways and affect several proteins regulating this process (Askew, Ashmun, Simmons, & Cleveland, 1991; Evan et al., 1992; Klefstrom, Verschuren, & Evan, 2002). MYC activation leads to induction of $p19^{ARF}$, which inhibits MDM2, leading to the stabilization of p53. p53 induces pro-apoptotic modulators, such as NOXA and PUMA, and trigger apoptosis (Nakano & Vousden, 2001; Villunger et al., 2003; Zindy et al., 1998). In addition, MYC induces BAX, which trigger cytochrome c release from the inner

mitochondrial membrane, and initiates apoptosis via the intrinsic pathway (Soucie et al., 2001). Oncogenic MYC can also prime the mitochondria for TRAIL-induced caspase-8 signals through a mechanism involving activation of BAK, which leads to activation of BAX and ultimately apoptosis (Nieminen, Partanen, Hau, & Klefstrom, 2007). Another mechanism in which MYC triggers apoptosis in a p53-independent manner is via the induction of BIM, a BH3-only pro-apoptotic factor (Egle, Harris, Bouillet, & Cory, 2004). BIM induction render the cell susceptible to FAS and TNF-α mediated cell death. In addition to the induction of pro-apoptotic factors, MYC has been reported to suppress anti-apoptotic factors, such as BCL-2 and BCL-XL, which also contributes to its apoptotic effect (Eischen, Woo, Roussel, & Cleveland, 2001; Galardi et al., 2016). It is worth noting that the ability of MYC to induce apoptosis is dose dependent. High expression levels of MYC strongly induces apoptosis, whereas moderate MYC levels was reported to enhance the rate of cell proliferation while exhibiting low apoptotic index (Murphy et al., 2008). Nevertheless, tumor cells can circumvent the effect of high MYC expression by upregulating anti-apoptotic factors or through other mechanisms of apoptosis suppression (Schmitt & Lowe, 2001). For instance, overexpression of BCL-2 and p53 mutations/deletions are common during MYC-driven cancer development, which provide cancer cells with an escape route and thereby allow MYC overexpression and proliferation without triggering apoptosis (Meyer & Penn, 2008).

MYC has also been linked to cellular senescence. The role of MYC in senescence is complex and may depend on the cell type and the underlying genetic makeup of the tumors. MYC was shown to suppress $BRAF^{V600E}$ or $NRAS^{161R}$-induced senescence in human melanoma cells, as MYC overexpression in these cells blocked senescence induction (Zhuang et al., 2008). Similarly, overexpressing MYC in rat embryonic fibroblasts (REFs) abrogated HRAS-induced senescence, which was countered by $p27^{kip1}$ overexpression (Hydbring et al., 2010). The ability of MYC to counter RAS-induced senescence was shown to be dependent on CDK2, via MYC phosphorylation by CDK2 on Ser-62. Additionally, importance of MYC in suppressing oncogenic-induced senescence was demonstrated *in vivo* using mouse lung models driven by $BRAF^{V600E}$ (S. Campaner et al., 2010; Juan, Muraguchi, Iezza, Sears, & McMahon, 2014; Tabor, Bocci, Alikhani, Kuiper, & Larsson, 2014). MYC suppression of senescence induced by RAS or $BRAF^{V600E}$ in cultured cells and *in vivo* was linked to suppression of $p21^{CIP1}$ and $p16^{INK4a}$ mediated by MYC (Hydbring & Larsson, 2010; Tabor et al., 2014). However, MYC has also been reported to induce senescence under certain conditions. For instance, Werner syndrome gene (WRN)-deficient fibroblasts underwent senescence following MYC overexpression in a similar way as CDK2-deficient cells (S. Campaner et al., 2010; Grandori et al., 2003). Conversely, MYC expression was unable to suppress RAS-induced senescence in normal human fibroblasts, regardless of p53 status (Zhang et al., 2018). These studies suggest that the role of MYC in regulating senescence is dependent on other factors that dictate the response to MYC overexpression with respect to senescence induction or suppression.

1.3.6 MYC and its role in tumor immunity

In recent years, a new role of MYC in tumor development is emerging. Aside from its promotion of cellular proliferation and growth discussed above, MYC has been

implicated in facilitating cancer cell evasion of immune surveillance. Early studies by Rakhra et al. in Dean Felsher's lab showed that MYC inactivation resulted in enhanced recruitment of CD4 T cells into the tumor microenvironment and tumor regression in a MYC-driven T cell acute lymphoblastic lymphoma (ALL) mouse model (Rakhra et al., 2010). In a follow up of the Rakhra study using a MYC-regulated Tet-off system in transgenic mouse model of hepatocellular carcinoma, Felsher's lab showed that MYC inactivation led to the downregulation of expression of two important immune modulators, PD-L1 and CD47, in the tumor cells (Casey et al., 2016). Both of these receptors are involved in cancer cell immune evasion mechanisms, as PD-L1 block CD8 cytotoxic T cell activation while CD47 protect cells from macrophage phagocytosis. In the same study, knockdown of MYC using shRNA or using the BRD4 inhibitor JQ resulted in similar downregulation of PD-L1 and CD47 expression in different human cancer lines. In addition, chromatin immunoprecipitation sequencing (ChIP-seq) analysis revealed that MYC bound directly to PD-L1 and CD47 promoters when highly expressed, indicating a direct regulation of these genes by MYC. Further, Atsaves et al showed that MYC regulate PD-L1 expression transcriptionally following JAK1/STAT3 activation upstream of MYC in ALK-driven anaplastic large-cell lymphoma cells (Atsaves et al., 2017). A role of MYC in the regulation of PD-L1 was suggested also in several other *in vitro* and *in vivo* studies, including reports from patient-derived xenografts, lung cancer, lymphomas as well as neuroblastoma driven by MYC or MYCN (E. Y. Kim, Kim, Kim, & Chang, 2017; Melaiu et al., 2017). Another study by the Klefström lab demonstrated that pharmacological reactivation of MYC-dependent apoptosis by AMPK and BCL-2/BCL-XL inhibitor treatment, followed by PD-L1 depletion induced immune infiltration to the tumor tissue and enhanced survival in a MYC-driven mammary breast cancer model, showing a synthetic-lethal MYC strategy involving the immune compartment (Haikala et al., 2019). Another study by Topper et al., also implicated MYC in immunosuppression and the exhaustion of CD8 T cells in a $KRAS^{G12D}$ lung adenocarcinoma model (Topper et al., 2017). Their work demonstrated that the dual inhibition of DNMTs and HDACs, by aza-cytidine and ITF-2357 respectively, resulted in downregulation of MYC, induction of both CCL5 and IFN-α/β signalling, culminating in the activation of T cell response. These studies highlight a new non-cell autonomous role for MYC during tumor development, in addition to its control of tumor proliferation and survival through intrinsic mechanisms.

The mechanisms by which MYC exerts its effect on the immune system are still not fully deciphered. To gain more insight on MYC's immunomodulatory role in cancer, Kortlever et al. evaluated changes in the tumor microenvironment in relation to MYC status using a $KRAS^{G12D}$/MYC-driven lung adenocarcinoma mouse model. MYC inactivation was shown to coincide with an influx of NK, B and T cells into the tumor area, as well as with rapid regression of tumor mass (Kortlever et al., 2017). These changes were attributed to CCL9 and IL-23 overexpression by the tumor cells, as the depletion of these immunomodulators negated the immunosuppressive ability of MYC in this model. However, the tumor cells did not show upregulation in PD-L1 in response to MYC activation in this case, instead increased PD-L1 expression was observed in the macrophage cell population. This observation contradicts previous findings by Casey et al., suggesting that MYC's modulation of the immune system differs depending on the tumor tissue of origin. One difference in the systems used that possibly could have

contributed to this discrepancy, is the different levels of MYC in the two systems, as Kortlever et al. used lower expression levels of MYC compared to the study by Casey et al. A recent study by Sodir et al., where the effects of MYC on the tumor stromal compartment and tumor development was investigated using a $KRAS^{G12D}$/MYC-driven pancreatic ductal adenocarcinoma mouse model, the authors showed that MYC activity promoted immune evasion (Sodir et al., 2020). However, the study showed clear differences in the immune cell's response to MYC activity in tumor cells between the pancreas and the lung tumors. For instance, MYC activation in the pancreas tumors led to the influx of B cells into the tumor periphery, which was opposite to what was observed in the lung adenocarcinoma model. This effect was attributed to the presence vs. lack of IL-23 signalling in the PDACs and lung adenocarcinomas, respectively (Kortlever et al., 2017; Sodir et al., 2020). Furthermore, the PDACs showed elevated expression of PD-L1 on the surface of the tumor epithelium, in contrast to the lung adenocarcinoma model where the induction of PD-L1 expression was detected on the resident macrophages. In addition, the recruitment of suppressor Ly-6B+ neutrophils and G-MDSC reported in PDAC model following MYC activation was not observed in the lung tumor model. MYC inactivation in the PDACs lead to a fast tumor regression, which was accredited to the activity of infiltrating NK cells. Using another PDAC model, Daniel Murphy's lab reported similar findings and provided some mechanistic insight on how MYC elicits its immune suppressive function. ChIP analysis in human PDAC cells suggested that MYC and MIZ-1 together bind to STAT1, STAT2, IRF5, and IRF7 promoters, thereby suppressing these genes (Muthalagu et al., 2020). Further, PDACs carrying a floxed version of MIZ1, which is unable to bind MYC, showed a significant enhancement in overall survival. The study also showed that depletion of CXCL13, which is secreted by a subset of macrophages, depletion of type I interferon receptor 1 (IFNAR-1) or of NK cells abrogated MYC's suppression of B- and NK cell infiltration into the tumor area. Additionally, a recent study by Swaminathan et al. showed that MYC block NK maturation via the repression of STAT1/2 and type I IFNs, leading to the impairment of NK cells maturation and function in a model MYC-driven T cell lymphoma (Swaminathan et al., 2020). Moreover, they demonstrated that the administration of IFN-α rescued NK cell maturation and triggered their activation. The different studies discussed above demonstrate a clear role of MYC in immune suppression and evasion of killing by NK cells, resulting in tumor progression. Interestingly, these studies did not implicate T cells in the anti-tumor immune response following MYC inactivation, which one would have expected considering the PD-L1 regulation observed in some of these studies. Nevertheless, these studies clearly suggest that MYC participates in suppressing the immune system during cancer progression. However, further research is needed to deepen our standing of the mechanisms underlying this phenomenon and to clarify the role of different immune cells and immunomodulatory molecules involved in order to improve current cancer therapies.

1.3.7 MYC inhibition and cancer

Given the important role of MYC during the development of so many human cancers, it is considered an attractive target for cancer therapy. Several of the studies using different mouse tumor models mentioned above have demonstrated that MYC inactivation in established tumors resulted in tumor regression or hampering further tumor development.

The reason for this might be that MYC is involved in so many different processes crucial for cancer development and maintenance leading to "MYC addiction", further raising its value as promising target. Through the past two decades, many attempts have been made to develop inhibitors that can target MYC. This proved to be challenging, as certain characteristics of the MYC protein render it hard to target. In particular, the lack of enzymatic activity, the intrinsically disordered protein structure without defined ligand-binding sites makes it difficult for the design of highly specific and effective inhibitors. Nevertheless, many efforts are ongoing to develop therapeutics that can target MYC in cancer cells. These have been focused on different aspects of MYC regulation and function, ranging from blocking its interaction with important partner proteins, interfering with transcription or translation of MYC mRNA, to modulating its protein turnover. These different approaches have shown varying degrees of success as well as pitfalls, that can hopefully be used to refine the strategies to effectively target MYC in cancer in the future.

One of the approaches that have been investigated is the inhibition of MYC transcription by blocking different transcription regulators and epigenetic modulators, for instance BET proteins, histone deacetylases, histone methyltransferases and DNA methyltransferases that are known to participate in regulation of MYC expression. An example of this class of inhibitors are BET inhibitors and HDAC inhibitors. The BET family of proteins, such as BRD4, promote transcription and RNA pol II release via the recruitment of transcription elongation factor b (P-TEFb) to promoters to induce transcriptional elongation, particularly of genes involved in cell growth, including MYC (Z. Yang, He, & Zhou, 2008). Indeed, some cancer studies using the BET inhibitor JQ1 did show a reduction in the expression levels of MYC, leading to inhibition of tumor cell proliferation and tumor regression *in vitro* and *in vivo* (Bandopadhayay et al., 2014; da Motta et al., 2017; Delmore et al., 2011). However, JQ1 and other BET inhibitors did not have an effect on MYC expression in all cell types or tumor models, and its efficacy in clinical trials of refractory lymphoma, multiple myeloma, diffuse large B cell lymphoma among others were not overwhelming, as the treatment had limited effect and the patients showed tumor relapse (Bhadury et al., 2014; Doroshow, Eder, & LoRusso, 2017). This seemed to be caused by significant alterations in signalling pathways due to cellular adaptation to the inhibition of BRD4, resulting in resistance to treatment (Kurimchak et al., 2016). Despite these shortcomings, new studies reported an increased sensitivity of these resistant cells to kinase inhibitors, as the combination treatment of JQ1 and PI3K inhibitors induced cell death in pancreatic carcinoma and MYCN-amplified neuroblastoma cell lines (Andrews et al., 2017). These observations open the possibility to the use of combination treatment against MYC and other cooperating oncogenic drivers as a promising new treatment. Moreover, other BET inhibitors, such as AZD5153, ZEN-3694 and GSK525762 have shown encouraging results in MYC-driven tumor models and currently clinical trials are ongoing to evaluate its overall efficacy in prostate cancer and leukemia patients (Baumgart & Haendler, 2017; B. Li & Simon, 2013; Rhyasen et al., 2016). Another approach to inhibit MYC transcription aims at targeting DNA structures called G-quadruplexes, which are involved in gene silencing. In this strategy, the G-quadruplex structures residing in the nuclease hypersensitive element (NHE) III region of the MYC promoter are stabilized using small molecules, such as GQC-05 (Hurley, Von Hoff, Siddiqui-Jain, & Yang, 2006). Utilizing this mechanism, several studies have

shown significant reduction in MYC mRNA and protein expression, and downregulation of the MYC gene signature following treatment with these small molecule G-quadruplex stabilizers. Treatment with these molecules also led to cell cytotoxicity in non-Hodgkins lymphoma, renal cell carcinoma and Burkitt's lymphoma cells (Bouvard et al., 2017; Brown, Danford, Gokhale, Hurley, & Brooks, 2011; Das, Panda, Saha, & Dash, 2018). While this approach still requires further evaluation *in vivo* and in clinical trials to determine its overall potential and side effects, it nevertheless provides a new promising tool to combat MYC in cancer.

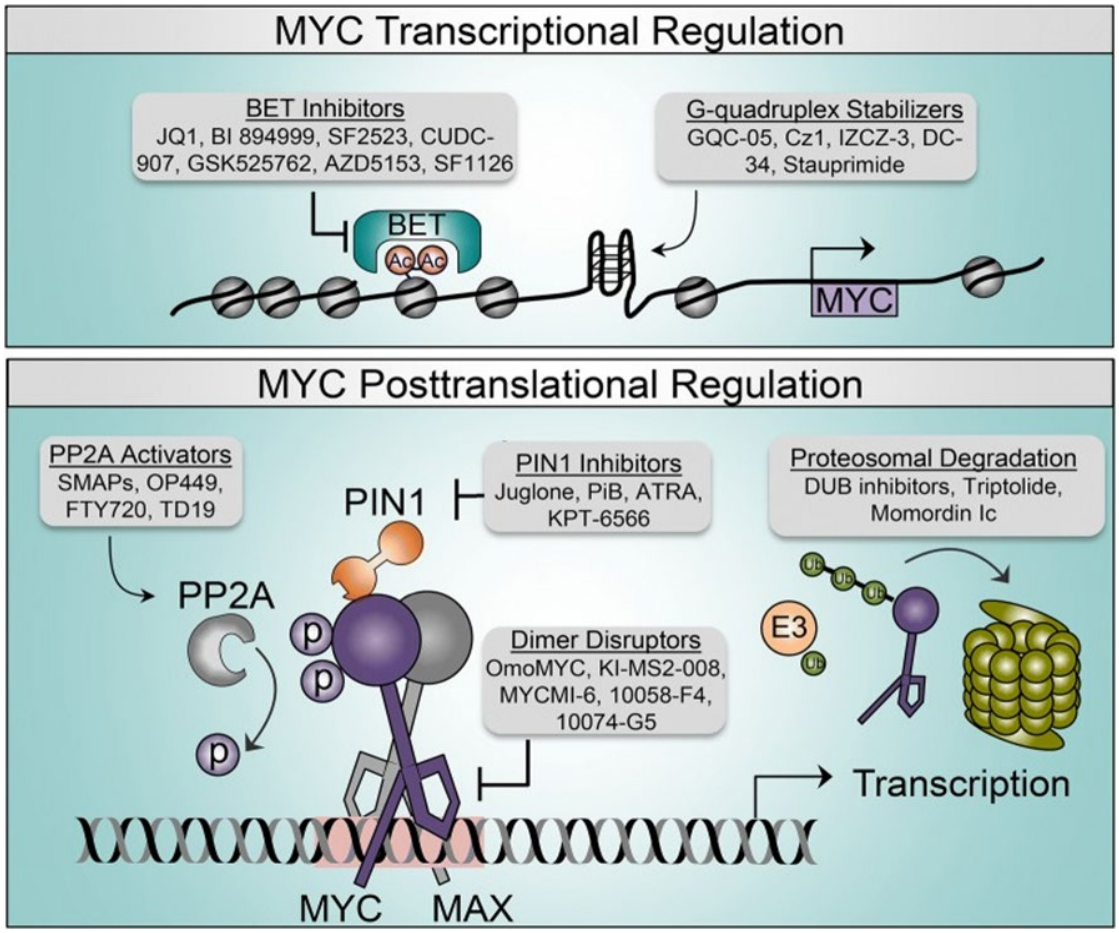

Figure 8: MYC regulatory pathways and therapeutic points of intervention. Different strategies to inhibit MYC and its functions. Adopted from Allen-Petersen, B. L. and Sears, R. C. et al., Mission Possible: Advances in MYC Therapeutic Targeting in Cancer. BioDrugs. 2019; 33: 539-553.

Another strategy to inhibit MYC centres around the posttranslational regulation and protein turnover of MYC. As discussed earlier, MYC undergoes many posttranslational modifications that regulate MYC protein stability and activity. One of the approaches in this strategy focuses on proteins involved in Ser-62 phosphorylation. Protein phosphatase 2A (PP2A), a serine/threonine phosphatase, plays an important role in regulating MYC function and protein stability by dephosphorylating MYC at Ser-62 (Arnold & Sears,

2008). Recently, small-molecule activators of PP2A (SMAPs), have shown promising results in reactivating PP2A and reducing MYC levels, among other oncogenes, in lung cancer cells (Kauko et al., 2018; Sangodkar et al., 2017). Additionally, work from Rosalie Sears' lab recently showed that the combination of DT1154, a SAMP, and INK128, an ATP-competitive mTORC1/2 inhibitor, synergistically reduced MYC levels and triggered apoptosis in breast cancer cells and in a PDAC xenograft mouse model (Allen-Petersen et al., 2019). The PP2A activation strategy to inhibit MYC prompts further investigation of its potential in pre-clinical and clinical studies. Another approach utilizing PP2A is through interfering with its cellular inhibitors, such as inhibitor-2 of protein phosphatase-2A (SET). For instance, studies using OP449, a molecule sequestering SET, led to the activation PP2A, decreased Ser-62 phosphorylation and blocked tumor growth in pancreatic and breast cancer cells (Farrell et al., 2014; Janghorban et al., 2014). Similarly, SET sequestering by OP449 induced a cytotoxic response in ABL inhibitor-resistant acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) cells, albeit the study did not investigate the effect on Ser-62 MYC levels (Agarwal et al., 2014). Additionally, targeting CDK2 to abrogate Ser-62 phosphorylation has been shown to trigger cellular senescence in cells and in MYC-driven AML and medulloblastoma mouse models, which we will discuss further in papers I and II (Bazzar et al., 2021; Hydbring et al., 2010). In contrast CDK2 depletion resulted in apoptosis induction in neuroblastoma cell lines, suggesting that different tumor types respond differently to CDK2 inhibition (Bolin et al., 2018) (Molenaar et al., 2009). Along the lines of utilizing CDK inhibitors to block MYC activity, the dual inhibition of CDK9 and MYC, via LDC000067 and BET inhibitor (BI 894999) respectively, inhibited tumor proliferation and induced apoptosis in models of AML and hepatocellular carcinoma (Gerlach et al., 2018; Hashiguchi et al., 2019; C. H. Huang et al., 2014). Similarly, blocking of CDK7, which is part of the transcription factor II (TFIIH) complex involved in RNA pol II phosphorylation and transcription initiation, led to the loss of the MYC transcription signature, reduction of tumor cell proliferation in MYC-amplified ovarian cancer cell lines and MYCN-amplified cancer cells and tumor regression in patient-derived xenograft tumor models (Chipumuro et al., 2014; McDermott et al., 2020; Zeng et al., 2018). Moreover, targeting of the ubiquitination/deubiquitination machinery involved in MYC regulation, such as FBXW7, SKP2, PIN1, HUWE1 and de-ubiquitinating enzymes (DUBs) can potentially be a useful tool to block MYC by reducing its activity or stability (E. Campaner et al., 2017; Peter et al., 2014; Tavana et al., 2016). For instance, Aurora kinase A (AURKA), which is involved in centrosome maturation and separation, binds MYCN and prevent its ubiquitination by FBXW7 (Otto et al., 2009). Studies from Brockmann et al. demonstrated that pharmacological inhibition of AURKA induced FBXW7-dependent MYCN degradation, leading to reduction in tumor proliferation and prolongation of survival in MYCN-amplified neuroblastoma xenografts and in the TH-MYCN neuroblastoma mouse model (Brockmann et al., 2013; Gustafson et al., 2014)

Finally, efforts have been made towards blocking MYC function by inhibiting its dimerization with its partner protein, MAX. As discussed earlier, MAX is crucial for MYC binding to E-box sequences and transcriptional activity and blocking MYC:MAX interaction can therefore abrogate MYC's activity in cells. First generation MYC-MAX dimer disruptors, including 10058-F4 and 10074-G5, inhibited tumor cell growth and

viability but suffered from off target effects and low *in vitro* and *in vivo* potency, with a high half-maximal inhibitory concentration (IC50) values ranging from 20 to 40 μM (Carabet, Rennie, & Cherkasov, 2018; Fletcher & Prochownik, 2015; McKeown & Bradner, 2014). Several efforts have been made to improve the specificity and efficacy of MYC:MAX inhibitors and recently some reports are showing more promising results. Our lab has identified two MYC:MAX inhibitors, MYCMI-6 and MYCMI-7, which displayed significantly lower IC50s and selectivity in blocking MYC:MAX dimerization and strong anti-tumor effects *in vitro* and *in vivo*, which I will discuss in paper III and IV (Castell et al., 2018). In addition, two other small molecule MYC:MAX inhibitors, named MYCi361 and MYCi975, that increased proteasome-mediated MYC degradation and showed strong downregulation in the MYC transcriptional program *in vitro* were reported in a recent study by Han et al. (Han et al., 2019). Furthermore, treatment with these compounds in allograft and xenograft tumor mouse models showed a significant reduction in tumor growth, upregulation of PD-L1 on tumor cells, increased immune infiltration and sensitization of tumors to anti-cancer immunity following PD-L1 depletion. Recently, a purified small Omomyc peptide that exhibit strong affinity to both MYC and MAX, and thereby block the dimerization between endogenous MYC and MAX, surprisingly exhibited good efficacy in penetrating the cell membrane and was capable of disrupting MYC-dependent transcription (Beaulieu et al., 2019). The strong anti-MYC capability of the Omomyc peptide was observed both in human cancer cell lines and in lung adenocarcinoma mouse models. Finally, an alternative approach using the small molecule KI-MS2-008, which stabilizes MAX:MAX homodimers, resulted in MYC degradation and downregulation of MYC target genes in cells, and exhibited inhibitory effects on tumor growth *in vivo* (Struntz et al., 2019). These different strategies demonstrate that MYC can be targeted by different means and provide encouraging strategies for the development of new effective anti-MYC cancer therapies.

2 Aims

The overall aim of this thesis was to increase the knowledge about MYC regulation and function and to evaluate different approaches of targeting MYC and its partners in cancer cells in order to find new therapeutic strategies to block MYC-driven tumor development in the future. In the first part of the thesis, I aim to elucidate the role of CDK2 in MYC-mediated senescence suppression and immune evasion during tumor development and to evaluate the potential of CDK2 depletion/inhibition as therapeutic principle to reverse these processes *in vivo*. In the second part of the thesis, I am to identify and characterize new small molecule MYC:MAX interaction inhibitors and evaluate the potency and selectivity with respect to blocking MYC-dependent tumor cell growth in cell cultures and *in vivo*.

In brief, the specific aims of each of the papers are the following:

Paper I: To investigate the efficacy of CDK2 pharmacological inhibition in inducing senescence and attenuating MYC-driven tumor development *in vivo* using a MYC/BCL-XL-driven acute myeloblastic leukemia (AML) mouse model.

Paper II: To unravel the role of CDK2 in $BRAF^{V600E}$/MycER-driven lung tumor development *in vivo* and its impact on MYC-mediated senescence regulation and immunosuppression using a conditional immunocompetent mouse lung tumor model.

Paper III and paper IV: To characterize the small molecule MYC:MAX inhibitors MYCMI-6 and MYCMI-7, and to evaluate their efficacy in inhibiting MYC-driven tumor growth in cell cultures and using mouse tumor models *in vivo* representing AML, breast cancer and MYCN-amplified neuroblastoma.

3 Results and Discussion

3.1 CDK2 depletion/inhibition induces senescence and immune cell infiltration, reduces tumor burden and prolongs survival in MYC-driven mouse tumor models (Papers I and II)

MYC is one the most frequently deregulated oncogenes in human cancer and plays a major role in tumor development. Overexpression of MYC is known to induce apoptosis, which acts as a barrier against tumor development, but tumor progression is often accompanied by loss of genes involved in apoptosis induction, such as p53 and PTEN or deregulation of proteins blocking apoptosis such as PI3K, RAS and BCL-2 or BCL-X_L. In addition to induction of apoptosis, MYC has been shown to suppress oncogene-induced senescence, a second important barrier against tumor development. Our previous work in REFs demonstrated that inhibition of oncogenic RAS- or BRAF-induced senescence by MYC is dependent on phosphorylation of MYC at Ser-62 by CDK2 (Hydbring et al., 2010). This observation potentially provides a new strategy to abrogate MYC function in cancer cells. To evaluate this strategy *in vivo*, we examined the effect of CDK2 depletion/inhibition on MYC-driven tumor development using two different mouse tumor models, MYC-driven AML (paper I) and lung tumors (paper II).

Paper I

In paper I, we utilized a MYC/BCL-XL-driven mouse myeloblastic leukemia model, described in (Högstrand et al., 2012), to evaluate the efficacy of CDK2 pharmacological inhibition in blocking tumor development and inducing senescence *in vivo*. To inhibit CDK2, we utilized the selective CDK2 inhibitors CVT313 and CVT2584 used in our previous work (Hydbring et al., 2010). First, we started by evaluating the effect of CDK2 pharmacological inhibition by CVT-2584 on cell proliferation and growth of MYC/BCL-XL-transduced murine HSCs in culture. CDK2 inhibition significantly reduced cellular proliferation and induced senescence, reflected by significantly higher SA β-gal positive cells treated with CVT2584. The reduction in tumor proliferation following CVT2584 treatment was not accompanied with induction of apoptosis, as observed following the treatment with DNA damaging agent, ellipticine. We next proceeded to evaluate CDK2 inhibition *in vivo*, by injecting the MYC/BCL-X_L-transduced HSCs into lethally irradiated BALB/c mice. Treatment with CVT2584 via i.p injection resulted in a moderate, but significant, enhancement in survival compared to mice treated with vehicle. In an attempt to improve survival further, we performed the same experiments using a higher CVT2584 dose, which resulted in a minor improvement of survival, in comparison to the vehicle. Further improvement in drug delivery and availability using minipumps did not have a profound effect on the overall survival. The aggressive nature of the initiated tumors and low bioavailability of the drug *in vivo* rendered higher margins of survival benefits challenging to achieve. Nevertheless, the pharmacological inhibition of CDK2 *in vivo* using CVT2584 significantly improved survival of the leukemic mice. Finally, we utilized an adjusted model to allow for slower AML progression, by injecting the MYC/BCL-X_L-expressing leukemic cells, harvested from leukemic mice, at lower cell number into sub-lethally irradiated mice. In these experiments, we evaluated the potential of CVT2584 in

comparison to the FDA-approved and senescence-inducing drug CDK4/6 inhibitor, palbociclib. The treatment with either of these inhibitors resulted in a significant, and comparable, enhancement in survival, compared to vehicle treated mice. Overall, these results demonstrate that CDK2 pharmacological inhibition *in vivo* was able to improve survival and delay tumor development.

We next investigated the effects on tumor load in the AML mice. Previous work using this model showed that the mice exhibit extensive infiltration of leukemic cells in the bone marrow, spleen and liver tissues. Using flow cytometry, we examined the percentage of tumor cells in these tissues, sorted by CD11b/Gr1 or internal markers GFP and YFP, and observed a significant reduction in the leukemic cell population in response to CVT2584 treatment in the bone marrow, spleen and liver at the day of sacrifice. Furthermore, the spleen weights of the mice were significantly lower than mice treated with vehicle. However, we did not observe clear differences in the histology of the spleen and liver tissues between the CVT- treated mice and the DMSO treated mice. These results show that CDK2 inhibition curbed the growth of the leukemic cells, contributing to improved overall survival. Next, we evaluated the molecular changes triggered by CDK2 inhibition in tumor-bearing tissues. Co-immunostaining of proliferation markers Ki-67 and Ser-10-phosphorylated histone H3 (p-H3S10) revealed a significant reduction in the proliferative index of tumor cells population in the spleen of CVT2584-treated mice. In addition, the reduction in Ki-67 and p-H3S10 was accompanied with reduction in the levels of cyclin A in the spleen. While we did not observe a reduction in MYC and BCL-XL protein levels, we observed reduction in phosphorylated Ser-62 MYC levels in response to CDK2 inhibition, which falls in line with our previous *in vitro* work. Based on our hypothesis, we assumed that the effect of CDK2 inhibition on tumor survival and proliferation was a consequence of senescence induction in response to anti-CDK2 treatment. We therefore proceeded to evaluate senescence through various markers in the spleen tissues. The spleen tissues from CVT2584-treated mice showed a significant increase in SA β-gal staining. This was accompanied by reduction of pRB phosphorylation and induction of $p21^{CIP1}$ and $p19^{ARF}$ protein levels, representing different markers of senescence. Furthermore, we observe an induction in $H3K9me^3$ histone marks in stained sections from CVT-treated mice, which was not observed in the vehicle-treated mice. In contrast, we did not observe signs of apoptosis following CVT-2584 treatment *in vivo*, in a similar fashion to our *in vitro* results.

Paper II

In paper II, we used a $BRAF^{V600E}$/MycER-driven mouse lung tumor model, to further evaluate CDK2 role in senescence suppression and its effect on MYC-related functions in tumor cells. These mice carry the oncogenic $BRAF^{V600E}$ allele and tamoxifen-regulated Myc-ER fusion protein, which is activated by CRE recombinase. Delivery of adeno-CRE virus containing the CRE recombinase enzyme into the lungs of the mice results in the recombination of these loci in the infected cells, leading to the activation of $BRAF^{V6OOE}$ and MycER expression (Tabor et al., 2014). These mice were cross-bred with conditional CDK2 knockout mice, where the CDK2 locus is flanked with LoxP sites, which are recognized and excised by the CRE recombinase enzyme, leading to CDK2 deletion. In the generated $BRAF^{V600E}$/MycER/$CDK2^{FL/FL}$ mice, inhalation of Ad-CRE therefore results in

CDK2 deletion, on top of $BRAF^{V6OOE}$ and MycER expression. Moreover, the activity of MycER is regulated through tamoxifen administration (TAM), which was delivered through the diet. Using this model, we first studied the consequences of CDK2 genetic deletion on the survival of the $BRAF^{V600E}$/MycER-mice. There was a significant enhancement in overall survival of mice with $BRAF^{V600E}$/MYC lung tumors lacking CDK2 ($CDK2^{FL/FL}$) compared to CDK2-proficient mice, with median survival of 127 days and 38 days respectively. The survival benefit of CDK2 genetic depletion was also improved in comparison with CDK2 wildtype mice expressing $BRAF^{V600E}$ without TAM (MycER off). The haematoxylin and eosin (H&E) histopathological analysis revealed that the enhancement in survival coincided with significantly lower tumor burden in the CDK2-depleted mice. To investigate the differences in tumor development, we studied the kinetics of tumor initiation and development at earlier time points. Our analysis showed a significantly lower tumor burden at 2, 3 and 4 weeks, following tamoxifen administration, in the $BRAF^{V600E}$/Myc-ER/$CDK2^{FL/FL}$ cohort compared to the $BRAF^{V600E}$/MycER cohort, indicating a delay in tumor development in response to CDK2 genetic depletion. In addition, our analysis showed a reduction in the number of overall tumors in CDK2-deficeint mice at the 2 weeks time point, with negligible difference at the 3 and 4 weeks time points. To validate these results, we used the CDK2 pharmacological inhibitor Cyc065 to block CDK2 activity in $BRAF^{V600E}$/MycER mice. In this experiment, Cyc065 was administrated orally for 2 weeks, starting 2 weeks after tamoxifen administration. The results show a similar reduction in tumor burden to the kinetic experiment between the Cyc065-treated and vehicle-treated mice. These results demonstrate that CDK2 genetic depletion enhances survival, delays tumor development and reduces tumor burden in $BRAF^{V600E}$/MycER lung tumors.

Next, we investigated the occurrence of senescence in CDK2 wt and CDK2 knockout $BRAF^{V600E}$/MycER tumors. Using Ki67 immunohistochemistry staining, our results showed a significant reduction in the proliferative index in $BRAF^{V600E}$/MycER tumors with depleted CDK2 as well as after pharmacological inhibition of CDK2. Evaluating other senescence markers, we observed an increase in p21 and $H3K9me^3$ staining in the CDK2-deficient cohorts, both at the endpoint and at the 3 and 4 weeks time points, as well as in Cyc065-treated mice. In addition, when investigating apoptosis using in situ cell death detection assay (TUNEL), our results showed a complete absence of apoptosis induction in all of our cohorts, further indicating that the differences observed between CDK2 wildtype tumors and CDK2 depleted tumors were a consequence of senescence induction. Moreover, analysis on whole lung lysates from the 4 weeks time point by immune blot showed an induction of p21 expression and reduction in pRB phosphorylation and PCNA, an S phase proliferation marker, in $BRAF^{V600E}$/MycER mice with deficient CDK2 compared with wildtype CDK2. Overall, our molecular analysis demonstrates that CDK2 depletion induced senescence in $BRAF^{V600E}$/MycER-driven lung tumors, which was correlated with prolonged survival and delayed tumor development.

To gain more insight into the molecular changes elicited by CDK2 ablation, we performed RNAseq analysis on lung tissues obtained from the 4-weeks time point. Our unsupervised hierarchical clustering analysis of the differential gene expression showed a discrete clustering of the upregulated and downregulated genes, and where MycER and CDK2 each show counteracting effects on gene expression. Gene enrichment and gene ontology

analysis of the gene expression data was then performed to gain more information on the different changes in pathways and processes involved in the observed phenotypes. Gene ontology analysis using the mouse reference genome, showed an upregulation in genes involved in metabolic processes in response to MycER activation by TAM compared to vehicle administration in $BRAF^{V600E}$/MycER mice with wildtype CDK2, as expected. Additionally, MycER activation led to downregulation of genes involved in the inflammatory response, consistent with recent publications regarding MYC role in cancer immunity (Casey et al., 2016; Kortlever et al., 2017; Muthalagu et al., 2020; Sodir et al., 2020). Comparing the gene expression of the $BRAF^{V600E}$/MycER groups with wildtype CDK2 vs. depleted CDK2 using the gene ontology database, we observed that CDK2 ablation led to induction of genes involved in different immune functions, including innate immunity and B cell activation. To confirm these results, we utilized the MetaCore gene expression database, which contains mouse sequencing data. Our analysis confirmed that CDK2 depletion in $BRAF^{V600E}$/MycER tumors resulted in an upregulation of the immune cell compartment. Additionally, analysis of differential gene expression using the PANTHER database showed an upregulation of innate immune response, B cell activation and phagocytosis. To investigate correlations with senescence-induced pathways, we analyzed the gene expression levels of different genes involved the senescent-associated secretory phenotype (SASP), as well as MYC signalling and other senescence-related processes, using the RNAseq reads. Our data showed differences in the expression pattern of SASP-related genes of relevance for the immune response. For instance, CXCL9, CXCL14 and IFN-γ receptor were upregulated in $BRAF^{V600E}$/MycER CDK2 KO mice induced with TAM, while CXCL1 and CSF2 expression was induced in corresponding TAM-treated CDK2 wildtype mice. Among these, CXCL9 and CXCL14 are chemoattractants that recruit and activate lymphocytes and monocytes respectively, IFN-γ receptor is expressed on macrophages and other cells, CXCL1 promotes angiogenesis and CSF2 is involved in granulocyte and monocyte maturation. In addition, the expression of negative immune regulators ENTDP1 (CD39), PD-L1 and SPP1 was downregulated in $BRAF^{V600E}$/MycER mice with depleted CDK2 compared to mice with wildtype CDK2. ENTDP1 is involved in the immune suppression activity exerted by regulatory T cells (Tregs), while PD-L1 is a well-known inhibitory checkpoint molecule involved in the suppression of CD8 cytotoxic T cells. In addition, SPP1 is also involved in promoting metastasis and pro-tumor immunity. Next, we examined the expression of different immune cell markers in the different groups. We observed an upregulation of the general macrophage marker CD68, in response to CDK2 loss, while T cell markers CD3g and CD3e, as well as MDSCs marker Ly6C were downregulated by MYC activation, regardless of CDK2 status. Worthy of note, we also observed an upregulation in M2-like macrophage marker MRC1 in the $BRAF^{V600E}$/MycER cohort with depleted CDK2, compared to $BRAF^{V600E}$/MycER cohort with wildtype CDK2. Finally, the analysis of the RNAseq reads showed an upregulation in the expression of senescent markers p21 and Lamin B1 in CDK2-depleted mice, confirming our results obtained from immunohistochemistry and protein immune blot analysis. Taken together, our gene expression analysis revealed that CDK2 loss led to apparent immune activation and diverse effects on the cytokines and chemokines expression profile in the $BRAF^{V600E}$/MycER-driven lung tumors.

Next, we opted to study if the phenotype and transcriptional changes observed in our lung mouse model can be recapitulated in human lung cancer cells. To do so, we utilized the

HCC364 lung cancer cell line, which carry a $BRAF^{V600E}$ mutation and in which we transduced MycER using a viral vector, thereby creating a similar model to the one used in our animal work. First, we evaluated senescence induction in response to CDK2 using siRNA knockdown. MycER was first activated by 4-hydroxytamoxfien (4-OHT) for 48 hrs, followed by CDK2 siRNA knockdown for 72 hrs. Our results showed that CDK2 knockdown in these cells led to senescence induction, characterized by increased SA β-gal activity and induction of p21 protein levels, exhibiting similar response to our previous results *in vivo*. We then proceeded to investigate the changes in the expression of different cytokines, chemokines and immune modulators in response to CDK2 knockdown, using RT-qPCR. We observed a downregulation of CXCL1, CSF2 and CCL-2 expression in response to CDK2 knockdown, irrespective of MycER status. Moreover, the expression of IL-6, IL-8, IL-1β and MMP3 were downregulated by CDK2 knockdown in MycER active cells. In contrast, several transcription factors involved in the regulation of the inflammatory response, including STAT3, STAT5A and IFN-γ were upregulated in response to CDK2 knockdown. Meanwhile, the expression of CXCL14, IL1A and interferon response factors IRF-5 and IRF-7 were downregulated following CDK2 knockdown. Finally, we observed a downregulation in the expression of the negative immune modulators ENTDP1 and PD-L1 expression following CDK2 knockdown, while CD47 expression was upregulated further in response to CDK2 knockdown. In summary, our results confirm that CDK2 knockdown induces senescence and alter the immune profile of HCC364-MycER human cell line, in a similar fashion to our *in vivo* results.

To validate our results obtained from the RNAseq data analysis and cell culture work, we examined the immune cell population in tumor tissues obtained from the different *in vivo* experiments using co-immunofluorescence staining. The tumor sections were stained for CD3 (T cell marker), PAX5 (B cell marker) and IBA1 (macrophage marker). The analysis of the stained sections at the end point showed a significant increase in T cell and macrophage infiltration in the lung tissues of $BRAF^{V600E}$/MycER mice with depleted CDK2. This infiltration was irrespective of MycER status in the tumors. In addition, further analysis revealed that the mice had significantly higher number of T cells and macrophages infiltrating the tumors. The analysis of the B cell population showed a significant increase in B cell infiltration in the lungs of CDK2 depleted mice with inactive MycER, while those with active MycER was higher but did not reach significance. The analysis of the tumor population at the 4 weeks time point showed a similar trend, albeit less pronounced compared to the end point experiment. Analysis by flow cytometry confirmed an increased presence of activated CD8 T cells in the lungs with CDK2-depleted tumors even with active MycER, while presence of activated NK cells increased in lungs CDK2 depleted tumors when MycER was inactive, but were suppressed by active MycER irrespective of CDK2 status. To assess the effect of MYC inactivation on the tumor burden and immune cell population, we carried an experiment where we treated $BRAF^{V600E}$/MycER CDK2 KO mice with TAM for 4 weeks, after which we either sacrificed the mice, or kept on them on TAM or normal diet for an additional 10 days. The histopathological analysis of the lung tumors showed a massive reduction in tumor burden following MYC inactivation for 10 days compared to 4 weeks group and the group with continued active MycER, with over 50% barely showing any signs of tumors in the lungs. We also observed a reduction in Ki67 positive tumor cells and in p21 staining in these mice. This was accompanied with a decrease in $H3K9me^3$ staining, suggesting a possible clearance of senescent cells in the

lungs. Furthermore, analysis of the different immune populations did not show any significant change in the overall infiltration of T cells and macrophages in the lung between the different groups. However, we observed a significant reduction in the B cell population in the TAM withdrawal group, compared to the control groups. Furthermore, analysis of the immune cell population within the tumor area showed a significant increase in macrophage infiltration following MYC withdrawal. Finally, our evaluation of apoptosis induction using in situ death assay did not indicate any presence of apoptotic cells in any of the experimental groups. Overall, the results show that MYC deactivation in CDK2-depleted tumors led to massive tumor regression and reduction in overall number of senescent cells, with no apparent apoptosis induction. These changes coincided with an increase in macrophages infiltration into the tumor area, suggesting a possible clearance of senescent tumor cells by macrophages in response to MYC withdrawal. Another possibility is that elimination of senescent tumor cells upon MYC withdrawal was the result of activation of cytotoxic T cells and/or NK cells, which then were phagocytized by macrophages.

Our work confirms that targeting CDK2 induces senescence in MYC-driven tumors *in vivo* and shows that this correlates with reduced tumor growth and proliferation, resulting in improved survival. It is therefore a promising concept that potentially can be utilized to combat MYC function is cancer. The pharmacological inhibition of CDK2 in our leukaemia model delayed tumor onset, triggered a senescence response and reduced tumor burden. The survival benefits were significant, but modest, which can be attributed to the aggressiveness of the model and the limitations with the CDK2 inhibitors available currently render it very difficult to achieve a very long durable response in this system. Similarly, CDK2 depletion in the $BRAF^{V600E}$/MycER-driven lung tumor model confirmed the importance of CDK2 in senescence suppression in tumors driven by MYC. The loss of CDK2 triggered senescence, inhibited tumor growth and significantly prolonged the survival. Furthermore, we uncovered a novel role for CDK2 in immunomodulation in the $BRAF^{V600E}$/MYC-driven lung tumors. This was difficult to evaluate in the AML model due to immune cell depletion after irradiation, which is necessary in this system prior to HSC transplantation. This immune modulatory function of CDK2 seems to affect different immune cells, including T cells, NK cells, B cells and macrophages. Interestingly, our flow cytometry analysis showed a significant increase in activated CD8 T cells in lungs in response to CDK2 depletion in tumors, irrespective if MycER was active or inactive. On the other hand, active MycER suppressed NK cell activation in agreement with previous reports (Kortlever et al., 2017; Sodir et al., 2020; Swaminathan et al., 2020), and this occurred irrespective of CDK2 status, while increased number of activated NK cells were observed after CDK2 depletion if MycER was inactive. This raises the question whether the tumor regression observed in CDK2-depleted tumors after deactivation of MYC, can be explained by combined T cell and NK cell killing of the lung tumor cells? If so, these observations suggest that the dual MYC and CDK2 inhibition might achieve a strong T cell- and NK cell-mediated response in MYC-driven tumors. This warrant further investigation. Worthy of mention, blocking CDK2 in MYCN-amplified neuroblastoma have been shown to induce massive apoptosis, and not senescence, suggesting a tissue-specific response in the effect and outcome of CDK2 inhibition (Molenaar et al., 2009). Regardless, our work demonstrates that CDK2 inhibition is a promising strategy in tumors dependent on MYC, such as medulloblastoma, B lymphomas and MYCN-amplified

neuroblastoma (Bolin et al., 2018; Molenaar et al., 2009). It can also be effective in tumors with cyclin E amplification and/or overexpression and tumors resistant to CDK4/6 inhibition, as CDK2 is reported to be involved in the resistance mechanism to CDK4/6 inhibitors (Herrera-Abreu et al., 2016). It also opens the possibility of using CDK2 inhibitors in combination with immunotherapies to boost the immune response. This work also warrants the need to develop more specific and effective CDK2 inhibitors as anti-cancer therapies, with a focus on MYC-driven tumors.

3.2 Small molecule inhibitors MYCMI-6 and MYCMI-7 bind MYC, selectively block MYC:MAX interaction, abrogate tumor cell growth and induce apoptosis in MYC-dependent tumors without killing normal cells (Papers III and IV)

The transcriptional regulation functions of MYC that are required for its cancer-promoting activity are dependent on the dimerization with its partner MAX. The crucial role of this dimerization for MYC biological activity prompted us to identify and characterize inhibitors that can block the interaction between MYC and MAX, thus directly inhibiting MYC functions. To achieve this, we carried out a cell-based screen using the bimolecular fluorescence complementation (BiFC) assay. In this assay, full-length MYC and MAX were fused to the non-fluorescent C- and N-terminus fragments of yellow fluorescent protein (YFP), respectively, which when brought in close proximity due protein-protein interactions restore the YFP fluorescence signal (Grinberg et al., 2004; Hu et al., 2002). We co-transfected these constructs into HEK293 cells, and validated the assay by using a MYC construct lacking the bHLHZip domain (MYCΔbHLHZip) required for dimerization with MAX. While the full length MYC-fusion resulted in a clear positive fluorescence signal together with the MAX fusion protein, using the MYCΔbHLHZip-fusion together with the MAX-fusion did not produce any positive signal, highlighting the high specificity of the assay. We then proceeded to use this technique to screen a small library of 1990 chemical compounds from the NCI/DTP repository for substances that can inhibit MYC:MAX dimerization. 6 compounds, (MYCMI-2, MYCMI-6, MYCMI-7, MYCMI-9, MYCMI-11 and MYCMI-14), with over 40% reduction in MYC:MAX specific positive signal as potential inhibitors of MYC:MAX interaction were identified, and were termed MYC:MAX inhibitors (MYCMI). The BiFC results were further validated by the use of protein-fragment complementation assay (PCA) that utilizes split Gaussia princeps luciferase (GLuc) (Remy and Michnick, 2006). The results show that the all 6 compounds significantly decreased the luciferase signal at 25 μM compared to cells treated with previous MYC:MAX inhibitor 10058-F4 used at 64 μM. Analysis of the effect of these compounds on the MYC protein level showed that two compounds, MYCMI-7 and MYCMI-9, reduced MYC level, while the other compounds did not have any measurable effect.

Paper III

In paper III, we focused on MYCMI-6, MYCMI-11 and MYCMI-14 for further investigation. In order to evaluate the inhibitory effects of these compounds on the endogenous cellular MYC:MAX interaction, we utilized in situ proximity ligation assay (isPLA), which is used to study protein-protein interaction in cells. Our results show that

cells treated with MYCMI-6, MYCMI-11 or MYCMI-14 exhibited a significant reduction in fluorescent dots, representing MYC:MAX complexes, in comparison with DMSO, with less than 1.5 μM IC50 for MYCMI-6 and 6 μM IC50 for MYCMI-11 and MYCMI-14. These effects were not observed for FRA1:JUN interactions, bZip transcription factors interacting in a similar way, indicating that these compounds are indeed selective towards MYC:MAX complexes. Additionally, co-immunoprecipitation showed a clear reduction in MYC:MAX protein complexes as early as 3 hrs post treatment with MYCMI-6. Moreover, treatment with MYCMI-6 in U2OS-MycER cells significantly attenuated MYC transcriptional activity induced by 4-hydroxy-tamoxifen, as indicated by the significant reduction mRNA levels of MYC target genes, ODC1, RSG16 and CR2, while MYCMI-11 and MYCMI-14 had more mild inhibitory effects. Next, we proceeded to assess the ability of these inhibitors to directly inhibit the formation of the MYC:MAX heterodimers using recombinant bHLHZip portions of MYC and MAX proteins in microscale thermophoresis (MST) and surface plasmon resonance (SPR) assays. MST is a thermophoresis-based assay in which the ability of a fluorescently labelled molecule to move in a microscopic temperature gradient is measured. This mobility is subject to changes caused by binding to other molecules. In the SPR assay, the protein of interest is immobilized on a chip, and the ligand of interest is allowed to flow over the immobilized protein. Binding between the protein and the ligand causes a change in the surface plasmon resonance that can be measured (Schasfoort and Tudos, 2008). The MST results showed that all three compounds weakened recombinant MYC bHLHZip interaction with the fluorescently labelled recombinant MAX bHLHZip, compared with DMSO. Additionally, MYCMI-6 selectively inhibited MYC:MAX dimers with a K_d of 4.3 ± 2.9 μM, with only a minor effect on MAX:MAX dimers, suggesting a high level of selectivity for MYC:MAX dimers over MAX:MAX dimers. In the SPR assay, MYCMI-6 inhibited MYC bHLHZip:MAX bHLHZip dimer formation at an IC50 of 3.8+/-1.2 μM, while the MYC:MAX inhibitors 10058-F4 and KJ-Pyr-927 had little or no effect at 10 μM. To determine whether MYCMI-6 binds directly to MYC or MAX, we performed MST and SPR using recombinant MYC and MAX bHLHZip domains. We observed alterations in thermophoresis from 1 μM of MYC in a titration experiment, after preincubation with 3 μM MYCMI-6, while MAX failed to cause any change at these concentrations, nor did the control proteins BCL-XL and bovine serum albumin (BSA). SPR analysis using immobilized MYC bHLHZip showed a K_D value of 1.6 ± 0.5 μM, while the MYC:MAX inhibitors 10074-G5 and the 10058-F4 analogue #474 showed K_D values of 28 and 15 μM respectively. MYCMI-6 binding to control proteins MAX and MXD1 (MAD1), which both are very similar to MYC in structure, and to p53 and YFP was not measurable. These results demonstrate that MYCMI-6 binds directly and selectively to MYC with single digit μM affinity.

Our next step was to evaluate the potency of MYCMI-6, -11 and -14 in inhibiting the growth of MYC-driven tumor cells. To examine this, we used a panel of neuroblastoma cell lines with or without MYCN-amplification and Burkitt's lymphoma cells with MYC translocation. Our results show that MYCMI-6 efficiently suppressed the growth of MYCN-amplified Kelly, IMR-32 and SK-N-DZ neuroblastoma cells, with IC50 of 2.5-6 μM, while MYCN-non-amplified SK-N-F1, SK-N-RA and SK-N-AS neuroblastoma cells were less sensitive. Our results also show that MYCMI-6 strongly inhibited anchorage-dependent growth of MYCN-amplified neuroblastoma cells. Similarly, MYCMI-6 significantly inhibited growth of Burkitt's lymphoma cells with IC50s averaging at 0.5 μM.

Additionally, MYCMI-6 inhibited MYCN:MAX dimerization in neuroblastoma cells as observed by isPLA and significantly decreased the expression of MYCN target genes. Next, we evaluated the effect of MYCMI-6 on MYC-dependent cell growth. To study this, we utilized the Rat immortalized fibroblast cell line, designated as TGR-1, a MYC-null TGR-1 cell line, designated as HO15.19, and a MYC reconstituted HO15.19 cell line, designated as HOMYC3. We observed a sharp decline in viability of TGR-1 and HOMYC3 cells as measured by WST-1 assay in response to MYCMI-6 treatment, while MYC-null HO15.19 did not exhibit any effects at the concentrations used. These results show that MYCMI-6 mechanism of action is indeed MYC dependent. Moreover, computational analysis of IC50 of the NCI-60 human tumor cell lines database for MYCMI-6 showed that cells with higher MYC expression were significantly more likely to respond to MYCMI-6 than cells with low MYC expression. Furthermore, our evaluation of MYCMI6 effects on normal cells vs tumor cells showed that MYCMI-6 treatment induced apoptosis in neuroblastoma cells, while it was not cytotoxic for normal cells, such as IMR-90 and BJ normal human fibroblasts. Finally, treatment MYCMI-6 in MYCN-amplified SK-N-DZ xenograft mouse model showed a massive induction of apoptosis, necrosis, and vasculature hemorrhage, which was accompanied by reduction in tumor cell proliferation and in microvascular density. Importantly, analysis of MYC:MAX dimerization by isPLA in tumor tissue revealed a reduction in dimerization within the MYCMI-6 treated tumors compared to DMSO-treated tumors.

Paper IV

In paper IV, we proceeded to focus and characterize the small molecule inhibitor MYCMI-7. In a similar fashion to our approach in the MYCMI-6 paper, we validated the efficiency of MYCMI-7 in inhibiting MYC:MAX dimerization, its ability to bind MYC and MAX, and its effect on tumor cell growth and survival *in vitro* and *in vivo*, using different cancer cell lines and tumor mouse models. Following the initial analysis by BiFC assay, Gluc assay and western blot mentioned earlier, we validated the effect of MYCMI-7 on MYC:MAX interaction using isPLA in MCF7 breast cancer cells. The results showed a strong reduction in MYC:MAX interaction signal following treatment with 5 μM MYCMI-7 for 24 hrs. Moreover, a co-immunoprecipitation for MYC and MAX showed that MYCMI-7 reduced the level of MYC:MAX complexes as early as 1 hr post treatment, with increasing inhibitory effect on MYC:MAX interaction while no reduction of total MYC protein level occurred up to 4 hrs post treatment. Chromatin immunoprecipitation (ChIP) analysis in MCF7 breast cancer cells following 6 hrs of 5 μM MYCMI-7 treatment resulted in reduction in MYC association with the MYC target ODC1 gene promoter, starting at 2 hrs and steadily decreasing up to 24 hrs. The de-association of MYC from ODC1 promoter coincided with a reduction in ODC1 expression. To determine whether MYCMI-7 binds directly to MYC, SPR assay using a recombinant MYC bHLHZip protein domain immobilized on the chip demonstrated that MYCMI-7 binds to MYC in a dose-dependent manner, with a K_D of ~ 4 μM. These results provided evidence that MYCMI-7 binds MYC directly and rapidly, as well as specifically block MYC:MAX dimerization in cells and low μM concentrations.

When examining the effect of MYCMI-7 on MYC protein level following longer treatments (24-48 hrs), we observed a reduction in MYC and MYCN proteins levels in

different cancer cell lines. To investigate the mechanism behind this, we performed RT-qPCR analysis at different time points in MCF7 breast cancer cell line, following treatment with 5 μM MYCMI-7, which showed that MYCMI-7 treatment did not affect MYC mRNA levels. Next, we evaluated if MYCMI-7 decreased MYC protein level, and whether this involved SCF^{FBXW7} E3 ligase mediated-degradation. For this, HCT116 colon cancer cell line with deficient FBXW7 was used. To investigate the dynamics of MYC protein degradation by MYCMI-7, we performed cycloheximide (CHX) chase assay to examine MYC protein level, where CHX was added to block new protein synthesis following MYCMI-7 treatment after which the rate of decay of MYC protein was monitored. This assay provides information on rate turnover in the cell. Our results showed that MYC protein turnover was increased in FBXW7 wildtype HCT116 cells, but not in FBXW7-defecient HCT116 cells, following treatment with MYCMI-7. This effect was not due to a general increase in FBWX7 activity, since the protein levels of cyclin E, another FBXW7 target, was unchanged. Examination of MYC Thr-58 and Ser-62 phosphorylation, the binding sites for FBXW7, by western blot did not show any increase in response to MYCMI-7. In addition, expression of MYC in the T58A and S62A mutants was still reduced in response to the treatment. These results suggest that MYCMI-7-mediated downregulation of MYC protein levels were dependent on FBXW7, but through an indirect mechanism and not through the classical FBXW7 mechanism.

We next evaluated the effect of MYCMI-7 on MYC-dependent cell growth. To study this, we utilized similar approach to the one described in paper III, using the TGR-1, H015.19 and HOMYC3 cell lines. Similar to MYCMI-6, treatment with MYCMI-7 for 48 hrs showed a drastic decline in viability of TGR-1 and HOMYC3 cells as measured by WST-1 assay, with IC50s of 2 μM, while MYC-null HO15.19 remained unaffected, even at higher MYCMI-7 concentrations. Treatment with ellipticine, a DNA intercalator/Top2 inhibitor with similar structure as MYCMI-7, uniformly reduced the viability of all three cell lines. Next, we continued to evaluate MYCMI-7 ability to inhibit the growth of MYC-driven cancer cell lines. MYCMI-7 exhibited significantly stronger inhibitory effects on cell growth and viability in MYCN-amplified compared to MYCN-non-amplified neuroblastoma cells. Strong reduction in tumor cell growth was also observed in Burkitt's lymphoma cell lines upon treatment with MYCMI-7. Additionally, analysis of MYCMI-7 IC50 and expression data for the NCI-60 diverse human tumor cell line panel, described previously in paper III, showed a strong correlation between the response to MYCMI-7 and MYC cellular levels; 63% of cell lines with high MYC expression were responsive to MYCMI-7 compared to only 21% responders in cells with low MYC levels. Moreover, we investigated the ability of MYCMI-7 to block transformation of primary rat embryonic fibroblasts (REFs) transfected with RAS and MYC. The results showed that MYCMI-7 blocked foci formation and colony formation in semi-solid medium at a concentration of 0.5 μM. Similar IC50 value was observed for 3D cultures of MYC-amplified SK-N.DZ neuroblastoma cells. We next studied changes in global mRNA expression elicited by MYCMI-7 treatment using RNAseq analysis in MCF7 breast cancer cells. Gene set enrichment analysis (GSEA) showed downregulation of the MYC and E2F target gene profiles following MYCMI-7 treatment. This was accompanied by upregulation of genes involved in the inflammatory response, such as NFκB, consistent with recent reports implicating MYC in immune suppression in different tumors. These results show that MYCMI-7 exhibit strong MYC-dependent anti-tumor growth capabilities.

To study the effect of MYCMI-7 on the cell cycle, we utilized the P493-6 B cell line containing a doxycycline-regulated MYC, as well as normal REFs. Cell cycle analysis by flow cytometry showed an accumulation in G1 in P493-6 cells treated with MYCMI-7, accompanied with a increase in apoptotic sub-G1 population. In contrast, MYCMI-7 treatment induced cell cycle arrest in normal REFs but no apoptosis, as evident by the accumulation of cells in G1 without signs of a sub-G1 population. Importantly, MYCMI-7 treatment did not cause apoptosis in immortalized MYC-deficient Rat1 HO15.19 cells, but induced apoptosis in a dose-dependent manner in parents TGR1 cells and the HOMyc3 MYC-deficient cells reconstituted with MYC. Note that MYCMI-7 reduced cell proliferation and metabolic activity of human normal dermal fibroblasts (HNDF) and primary normal human epidermal melanocytes (NHEM) but did not reduce viability or induced apoptosis in these cells. Overall, MYCMI-7 halted the proliferation and caused cell cycle arrest in both normal and tumor cells but lead to apoptosis only in tumor cells and immortalized cells, thereby showing a good therapeutic window.

Giving the structural similarities between MYCMI-7 and ellipticine, which has been described as a topoisomerase 2 (Top2) inhibitor and DNA intercalator, we sought to investigate if MYCMI-7 inhibits Top2 and whether this can explain its anti-tumor effects. To do so, we first evaluated if MYCMI-7 can inhibit Top2 activity *in vitro* using Top2 decatenation assay. In this assay, Top2 decatenate kinetoplast DNA, converting interlocking DNA rings into individual rings that can be examined with agarose gel electrophoresis. Our results show that MYCMI-7 exhibited inhibitory effects on Top2 activity at a concentration of 30 μM, reaching complete inhibition at 100 μM. In comparison, the Top2 inhibitor doxorubicin (DOX) exhibited this effect starting at 3 μM and reaching complete inhibition at 10 μM, while ellipticine and the topoisomerase 1 (Top1) inhibitor camptothectin did not show any inhibitory effect on Top2 activity at any given concentration. Moreover, our *in vitro* examination of MYCMI-7 ability to intercalate with the DNA showed that it did do so at low μM concentrations in a similar manner as ellipticine. However, in contrast to ellipticine, this did not result in any induction of p53 or ATM phosphorylation, or reduction in MYC mRNA levels in cells at active concentrations of MYCMI-7. Moreover, depletion of p53 in HCT116 cells did not affect MYCMI-7-induced growth inhibition/viability. To further evaluate if MYCMI-7 activity is dependent on Top2, we performed isPLA on HCT116-TIR-AID cells, which contain an auxin-regulatable Top2, in which auxin treatment results in rapid degradation of Top2. The cells were pre-treated with auxin to deplete Top2 and then subjected to MYCMI-7 treatment for 6 hrs, before isPLA examination. The results demonstrated that Top2 depletion did not affect MYC:MAX dimerization nor did it abrogate the inhibitory effects of MYCMI-7 on MYC:MAX. We further validated these results by siRNA-mediated knockdown of Top2 in MDA-MB-231 breast cancer cell line. Top2 knockdown did not abolish MYCMI-7's ability to decrease cell viability, nor did it change the IC50 of MYCMI-7, arguing against a role of Top2 in MYCMI-7 mechanism of action. Collectively, these results suggest that MYCMI-7 does not primarily induce DNA damage and its MYC inhibitory effects are not dependent on Top2 or p53.

In the final part of the project, we evaluated MYCMI-7's anti-tumor activity in patient-derived tumor cells in culture and in mouse tumor models *in vivo*. First, we investigated the

efficacy of MYCMI-7 using a collection of 42 primary patient-derived glioblastomas representing different subtypes. MYCMI-7 treatment strongly reduced the growth/viability of these cells at a concentration around 1 μM, regardless of the tumor subtype. Additionally, MYCMI-7 inhibited the growth of several primary patient-derived AML cells in a dose-dependent manner, with IC50 ranging between 0.15-1.3 μM, showing significantly stronger inhibitory effects than 10058-F4, JQ1 and cisplatin, a drug used in the clinic for AML patients. Next, MYCMI-7 was validated in several MYC-driven mouse tumor models. Using the MYC/BCLXL-driven acute myeloid leukemia (AML) model described in paper I, we evaluated the effects of MYCMI-7 treatment on tumor load, progression, and overall survival. At day 15 post tumor cells injection, we observed significantly lower tumor load in the spleen and bone marrow of MYCMI-7-treated mice compared to the vehicle-treated cohort, indicating a delay in tumor progression in response to MYCMI-7 treatment. Similarly, we observed significantly lower tumor load in the bone marrow and spleen at the survival endpoint. Additionally, mice treated with MYMI-7 had less histologically disorganized spleen structure, with less infiltrating leukemic cells, compared to vehicle-treated mice. Importantly, MYCMI-7 treatment was tolerable, as body weight of treated mice did not get affected by the treatment. The tumor cells in the spleen of MYCMI-7-treated mice also exhibited lower levels of MYC expression than control mice. However, this obvious response to MYCMI-7 did not improve the overall survival of the mice, which might be attributed to extreme aggressiveness of these tumors along with suboptimal delivery and limited bioavailability of MYCMI-7 *in vivo* using i.p route. In addition, our evaluation of MYCMI-7 turnover in the plasma of mice showed a rather short half-life of 1.5 hrs, which explains part of the poor effect on survival in this aggressive model. In summary, MYCMI-7 inhibited MYC/BCL-XL-driven tumor growth *in vivo* with tolerable side effects. Finally, we examined the anti-tumor effect of MYCMI-7 in mouse xenograft tumor models, using human breast cancer and MYCN-amplified neuroblastoma cell lines. MYCMI-7 was delivered via intra-tumoral injections, every 4 days, to avoid the MYCMI-7 delivery issues observed after i.p injection in the AML model. The results showed that MYCMI-7 inhibited tumor growth and improved the overall mouse survival in both xenografts models. In addition, immunohistochemistry analysis of the MDA-MB.231 tumor sections revealed that MYCMI-7 treatment reduced MYC and Ki67 expression, and induced apoptosis as evidenced by annexin V staining and the expression of caspase 3. These changes were also accompanied by reduction CD31 expression, indicating a decrease in microvasculature. Furthermore, we observed massive apoptosis and necrosis and strong reduction in MYCN expression in MYCN-amplified SK-N-DZ tumors in response to MYCMI-7 treatment.

In summary, we observed that MYCMI-6 and MYCMI-7 bound directly to MYC *in vitro*, and inhibited MYC:MAX protein interaction in cells at low μM concentrations. Both of these inhibitors blocked tumor cell growth and induced cell death in tumor cells in a MYC-dependent manner, while resulting in growth arrest, without cytotoxicity, in normal cells. Furthermore, MYCMI-6 and/or MYCMI-7 inhibited tumor growth and reduced MYC/MYCN activity/expression in mouse tumor models of AML, breast cancer and neuroblastoma without giving severe side effects. In the xenograft models, MYCMI-6 and MYCMI-7 triggered apoptosis/necrosis and MYCMI-7 improved overall mouse survival. The latter remains to be investigated for MYCMI-6. Enhancement of MYCMI-6 and MYCMI-7 bioavailability *in vivo* and additional insight into the mechanisms of action of

these molecules are important steps for further development towards a potent anti-MYC drug for cancer treatment of patients in the clinic. The efficiency of both compounds in blocking MYC:MAX dimerization in the different cell lines we used is quite comparable and more potent than any of the previous MYC:MAX inhibitors, such as 10058-F4, 10074-G5, MYCi361, MYCi975, KJ-Pyr-9 and others (Clausen et al., 2010; Han et al., 2019; Hart et al., 2014; H. Wang et al., 2007). Similarly, MYCMI-6 and MYCMI-7 affinity for MYC is superior to that of 10074-G5, 10058-F4, and F4 analogue #474 reported in other studies (Müller et al., 2014). Only MYCi361 and MYCi975 were reported to have similar affinity to MYC, although the method used to assess that is different and indirect, which is difficult to compare (Han et al., 2019). Despite the similarities in the outcome of MYCMI-6 and MYCMI-7 treatment regarding tumor growth, they appear to operate through different mechanisms. Unlike MYCMI-6, MYCMI-7 decreased MYC protein level in different cell lines. This is similar to what was observed in response to treatment other MYC:MAX inhibitors, such as 10058-F4, 10074-G5 and sAJM589 (Choi et al., 2017; Clausen et al., 2010; Müller et al., 2014). This effect of MYCMI-7 on MYC levels, which appears to depend on FBXW7, is yet to be understood. For instance, MYCMI-7 did not affect the phosphorylation status of Thr-58 or Ser-62 on MYC, which plays an important role in FBXW7-mediated MYC degradation. In comparison, MYCi361 and MYCi975 treatment triggered MYC phosphorylation at Thr58 and subsequent degradation of MYC (Han et al., 2019). The difference between MYCMI-6 and MYCMI-7 with respect to MYC turnover can be possibly due to a difference in the binding mode and its effect on MYC protein folding. It's also possible that MYCMI-7 has off target effects that affects MYC turnover, which requires further investigation. We consider the former possibility more likely considering that many other MYC:MAX inhibitors reduced MYC levels. Moreover, a recent study by Mathsyaraja et al. showed that MYC protein levels were significantly reduced upon MAX deletion in normal and Eμ-MYC premalignant B cells, suggesting that the interaction with MAX stabilizes MYC (Mathsyaraja et al., 2019). On the other hand, the fact that MYCMI-6 does not affect MYC protein level provide a molecular tool to evaluate MYC function independent of MAX. Collectively, both of these compounds inhibited MYC:MAX interaction selectively, abrogate MYC-dependent tumor cell growth and induce apoptosis in cell cultures and *in vivo*, without affecting viability of normal cells.

4 Summary and Conclusions

MYC have been shown to be crucial for many different aspects of tumor development, contributing to most of cancer hallmarks, and deregulation of MYC is often associated with aggressive disease, resistance to treatment and poor outcome in human cancer. One of the reasons for this is that MYC plays such an important role as a transcription factor in many essential cellular processes of relevance for tumor development. This thesis has paid particular interest in two processes that relatively recently was shown to be under MYC regulation: cellular senescence and immune modulation. The growing evidence of MYC playing a central role in cancer and therapeutic outcome sparked the interest in developing different strategies to block MYC functions. The disordered nature of the MYC protein structure and its lack of enzymatic activity or druggable pockets, however, render this very challenging, and MYC has been considered "undruggable". To block MYC and its functions, different approaches have been suggested, ranging from blocking MYC transcription, interfering with its posttranslational modifications to inducing its protein degradation. Interestingly, to function as a transcription factor, MYC needs to interact with a number of partner proteins. Hence, targeting the interaction between MYC and partner proteins or targeting druggable enzymatic activities of partner proteins, when possible, are plausible ways of interfering with MYC function. As part of these efforts, this thesis work centres around evaluating these two different strategies to inhibit MYC functions and develop new treatments for cancer therapy.

In paper I and II, we focused on the ability of MYC to block oncogene-induced senescence, and if it is feasible to target this function as anti-cancer treatment. Since MYC-mediated senescence suppression was previously shown to rely on its phosphorylation by CDK2, we investigated whether targeting CDK2 could halt MYC-driven tumor development *in vivo*. We demonstrated that inhibiting CDK2, either pharmacologically or genetically, indeed induced senescence in MYC-driven mouse AML and lung tumor mouse models, reduced tumor burden and increased survival. In addition to senescence induction, our data suggest that CDK2 depletion reverses MYC-mediated immune suppression in lung tumors, resulting in infiltration and activation of adaptive and innate cells into the tumor area. The exact nature of different immune subpopulations involved and their activities in relation to MYC and CDK2 status are yet to be dissected, which will provide additional insight on MYC regulation of the immune response during tumorigenesis. We conclude that CDK2 inhibition is a promising strategy for future anti-MYC cancer therapies and warrant a need for the development of more specific and potent CDK2 inhibitors. Further, the role of CDK2 in MYC immunomodulatory functions has a promising potential to be exploited for possible combination treatment with immune therapy.

In paper III and IV, we focused on identification and characterization of small molecule inhibitors that block the dimerization of MYC with its obligatory partner, MAX. Two compounds, MYCMI-6 and MYCMI-7, bound MYC directly *in vitro* and showed strong and selective inhibitory effect for MYC:MAX endogenous interaction in cells at low micromolar concentrations. Further, the two compounds efficiently inhibited MYC-dependent tumor cell growth in cell cultures and in mouse tumor models *in vivo* with minimal side effects. The results obtained from MYCMI-6 and MYCMI-7 are

encouraging and warrant further investigation with respect to their mechanism of action and to the improvement of their efficacy and bioactivity for further pre-clinical/clinical development. In conclusion, these two approaches to interfere with MYC function showed promising results and can potentially pave the way for new advancements in anti-MYC cancer therapy.

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